University of Helsinki
Institute of Clinical Medicine
Department of Surgery, Department of Vascular Surgery
Helsinki University Central Hospital
Helsinki, Finland

CAROTID SURGERY

A POSSE AD ESSE NON VALET CONSEQUENTIA

Pirkka Vikatmaa

ACADEMIC DISSERTATION

To be publicly discussed with the permission of the Medical Faculty of the University of Helsinki, in Auditorium 2 of Biomedicum, Helsinki University, Haartmaninkatu 8, Helsinki on December 16th, at noon.

Helsinki 2011

ISBN 978-952-10-7392-2 (paperback)
ISBN 978-952-10-7393-9 (pdf)
http://ethesis.helsinki.fi
Unigrafia, Helsinki 2011

YMPÄRISTÖMERKKI
MILJÖMÄRKT
441 697
Painotuote

Supervised by: Professor Mauri Lepäntalo
University of Helsinki and
Department of Vascular Surgery
Helsinki University Central Hospital
Helsinki, Finland

and

Docent Maarit Venermo
University of Helsinki and
Department of Vascular Surgery
Helsinki University Central Hospital
Helsinki, Finland

Reviewed by: Professor Markku Kaste
University of Helsinki and
Department of Neurology
Helsinki University Central Hospital
Helsinki, Finland

Professor Ari Harjula
University of Helsinki and
Department of Cardiothoracic Surgery
Helsinki University Central Hospital
Helsinki, Finland

Discussed with: Professor A. Ross Naylor
University of Leicester
Department of Cardiovascular Sciences
Leicester Royal Infirmary
Leicester, United Kingdom

To Michelle, Henri, Lauri, William, Nicole, Tuomas and Leena

CONTENTS

LIST OF ORIGINAL PUBLICATIONS

I Taha AG, Vikatmaa P, Soinne L, Thabet BA, Lepäntalo M. A comparison of carotid surgery in Northern Europe and Northern Africa. World J Surg 2010;34:362–367.

II Taha AG, Vikatmaa P, Albäck A, Aho PS, Railo M, Lepäntalo M. Are adverse effects reported comparable in different registries? Eur J Vasc Endovasc Surg 2008;35:280–285.

III Vikatmaa P, Sairanen T, Lindholm J-M, Capraro L, Lepäntalo M, Venermo M. Structure of delay in carotid surgery - an observational study. Eur J Vasc Endovasc Surg 2011;42:273-279.

IV Vikatmaa P, Mitchell D, Panduro Jensen L , Beiles B, Björck M, Halbakken E, Lees T, Menyhei G, Palombo D, Troëng T, Wigger P, Venermo M. Variation in clinical practice in carotid surgery in nine countries 2005–2010. Lessons from VASCUNET and recommendations for the future of national clinical audit. Eur J Vasc Endovasc Surg. Submitted.

V Vikatmaa P, Mäkitie AA, Railo M, Törnwall J, Albäck A, Lepäntalo M. Midline mandibulotomy and interposition grafting for lesions involving the internal carotid artery below the skull base. J Vasc Surg 2009;49:86–92.

ABBREVIATIONS

AFX	amaurosis fugax
ACAS	Asymtomatic Carotid Atherosclerosis Study
ACST	Asymptomatic Carotid Surgery Trial
CAS	carotid angioplasty and stenting
CCA	common carotid artery
CEA	carotid endarterectomy
CETC	Carotid Endarterectomy Trialists Collaboration
CREST	Carotid Revascularization Endarterectomy vs. Stenting Trial
DD	duplex doppler ultrasound
ECA	external carotid artery
ECST	European Carotid Surgery Trial
ESVS	European Society for Vascular Surgery
FMD	fibromuscular dysplasia
HDR	hospital discharge registry
HUCH	Helsinki University Central Hospital
HUS	hospital district of Helsinki and Uusimaa
ICA	internal carotid artery
ICD-10	International Statistical Classification of Diseases, 10th revision
ICSS	International Carotid Stenting Study
M&M	morbidity and mortality
mRS	modified Rankin scale score
NASCET	North American Carotid Surgery Trial
NNT	number needed to treat
NOMESCO	Nordic Medico-Statistical Committee
OIS	ocular ischaemic syndrome
PAF	thrombendarterectomy (ICD-10 code)
PAH	graft interposition (ICD-10 code)
PAN	patch angioplasty (ICD-10 code)
RCT	randomised controlled trial
SKT	symptom to knife time
TIA	transient ischaemic attack
VA	Veterans' Affairs Cooperative Study

ABSTRACT

Embolic material from atherosclerotic lesions in the carotid arteries is one of the main aetiological factors for ischaemic stroke. According to a large body of evidence, carotid endarterectomy (CEA) can prevent strokes, provided that appropriate inclusion criteria and high-quality perioperative treatment methods are utilised with low complication rates. From the patient's perspective, it is of paramount importance that the operation is as safe and effective as possible. From the community's point of view, it is important that CEA provision prevents as many strokes as possible.

In order to define the stroke preventing potential of CEA in different communities, a comparison between eight European countries and Australia was performed. A more detailed evaluation was performed in Finland, the United Kingdom and Egypt. It could be estimated that many potentially preventable strokes occur due to insufficient diagnostics and CEA provision. The number of CEAs should be at least doubled in Finland and the United Kingdom.

Clinical registries provide a possibility to monitor and analyse large amounts of patients and treatment episodes. The validity of registered data is crucial, because major health care planning and resource allocation decisions are often based on registered data. All CEA patients were identified from the local vascular registry of Helsinki University Central Hospital (HUCH) and HUCH discharge registry. The material was cross-matched on an individual patient level. A simplified search strategy led to a possibility of severe misinterpretation. The initial search provided 675 and 681 patients from the two different registries, but only 640 patients were included in both registries. Manual verification of the dataset revealed that 673 true CEAs had been performed from 2000 to 2005. The combined perioperative major morbidity and mortality (M&M) rate was 2.7%, corresponding well with earlier published data and international recommendations. There was no systematic avoidance of complications, and comparable M&M rates were obtained from both registers irrespective of the level of verification. Accordingly, both registers can be used in planning the CEA provision, provided that regular registry audits are performed.

Time delay from symptom to surgery (symptom to knife time, i.e. SKT) has been identified as one of the most important factors influencing the effectiveness of carotid interventions. One hundred consecutive symptomatic patients who had CEA were identified from routine clinical practice in HUCH. Referral and diagnostic pathways were analysed. SKT was calculated for each patient and divided into patient related, referral related, diagnostics related and operation queue related delays in order to identify the reasons for prolonged SKTs. The median SKT was 47 days (range 3–688 d.), which is far longer than the recommended 14 days. Only 11% of the patients were operated on within 2 weeks. The patients had a higher likelihood of reaching the target time if they were immediately referred to the same centre where the operation took place (OR 12.6, 95% CI 1.5–104, p=0.019). In conclusion, the primary diagnostic investigations for stroke, transient ischaemic attack (TIA) and amaurosis fugax patients should be performed on an emergency basis to reach the recommended SKT.

A total of 53,077 carotid procedures between 2005 and 2010 were registered in nine countries as part of the VASCUNET collaboration. There were clear differences in the theoretical stroke prevention effectiveness of CEA provision between the participating countries. 92.6% of the CEAs were performed according to European guideline recommendations. The proportion of patients who were operated on in a situation where no theoretical benefit to the patient could be expected varied from nil to 29.7% between the countries. The utility rate (N of interventions) of carotid procedures in one year per 100,000 inhabitants varied from 6.0 to 13.5 for all patients, and from 3.6 to 11.1 for symptomatic patients, revealing that there are major differences in the diagnostic and treatment processes of care between the countries. The reasons for these differences should be identified in order to be able to prevent more strokes. Carotid surgery was performed safely in all participating countries.

A previously unpublished method of combining medial mandibulotomy, neck incision and carotid artery interposition was carried out as a collaboration of maxillofacial, ear, nose and throat and vascular surgeons. Five patients were operated on with a technique that was feasible and possible to perform with little morbidity, but due to the significant risks involved, this technique should be reserved for carefully selected cases.

In stroke prevention, organisational decisions seem far more important than details in interventional procedures when surgery is carried out with low complication rates, as was the case in the present study. A TIA clinic approach with close co-operation between the on-call vascular surgeons, neurologists and radiologists should be available at all centres treating these patients. Patients should have a direct and fast admission to the hospital performing CEA.

INTRODUCTION

Carotid endarterectomy (CEA) for stroke prevention is probably the most standardised operation in vascular surgery. There are few other fields of surgery where decision-making is supported by so many randomised clinical trials (RCT). One of the main reasons for stroke is flow disturbance caused by embolism from an atherosclerotic lesion in the extracranial vessels, mainly in the internal carotid artery (ICA). RCTs, meta-analyses and guidelines have given the indications and limitations for CEA in many but not all clinical situations. The outcomes of RCTs can only partly be achieved in a community-wide clinical practice. The nature of CEA is preventive, and thus many of the operations performed do not actually help the patient operated on, although the CEA could statistically and clinically be well justified. It is not the case that all operated patients would eventually have suffered a stroke if they had not been operated on. However, all surgically treated patients face the risks of surgery. Therefore, physicians treating carotid atherosclerosis should be aware of their own results and the results of a large number of studies, use scientific data in daily decision-making and follow the national and international guidelines in their clinical practice.

Stroke is predominantly a disease of the elderly. The population of Finland and many other developed countries is aging fast, and stroke and its complications are getting more frequent despite the declining age-specific incidence and more effective treatment methods (Sivenius et al. 2010). During the past four decades, high-income countries have observed a worldwide 42% decrease in stroke incidence whereas the incidence in low to middle income countries has increased by more than 100% (Feigin et al. 2009). Modern cholesterol-lowering drugs (Cholesterol Treatment Trialists' (CTT) Collaborators 2005), antiplatelet treatments (Lemmens et al. 2009) and blood pressure lowering medications (Law et al. 2009) have reduced the incidence of stroke and may stabilise the plaque itself, but good medical care does not abolish the need of carotid surgery (Sillesen 2008; Lutz et al. 2011). At the same time, resources are getting scarcer, hospital administrations are getting more complex, centralisation is seen as a solution (Kantonen et al. 1998, Holt et al. 2007, Nazarian et al. 2008), and the workload of individual surgeons is restricted by legal working time limitations (Fletcher et al. 2005). Due to all these reasons, focus should be kept on the question of finding the most effective ways to prevent strokes. Invasive treatment should be preserved for those patients who are at a high risk of stroke. The benefits and risks of an invasive approach should be objectively evaluated for the benefit of the individual patient – not the surgeon or interventionalist (Naylor et al. 2009). It seems that the differences found in randomised studies are far smaller than the importance of effective organisations with short delays and the actual application of the results of RCTs in daily clinical praxis (Bunch and Kresowik 2004, Ploeg et al. 2010).

In addition to atherosclerosis, the carotid arteries may be affected by some other diseases, such as dissections, inflammation, genetic disorders, tumours and aneurysms (Nair et al. 2000; Sajid et al. 2007). For malignant tumours, the only curative treatment opportunity may be an operation in which all tumour material is excised (Wright et al.1996). Thus, extensive and potentially mutilating surgery is sometimes needed, but it should be practiced with great caution and only at specialised clinics. Extensive aneurysms and trauma to the carotid arteries may also need special surgical and/or endovascular techniques.

REVIEW OF THE LITERATURE

1. DISEASES AFFECTING THE CAROTID ARTERIES

1.1. ATHEROSCLEROSIS AND STROKE

Atherosclerosis is a disease affecting arterial blood vessels. It is a chronic inflammatory response in the walls of arteries which is in large part due to the accumulation of macrophage white blood cells promoted by oxygenated low-density lipoproteins. The aetiology and pathogenesis of atherosclerosis are complex. Vigorous research to clarify the importance and relations of different genetic, behavioural and environmental risk factors has been ongoing for decades. Dyslipidemia, hypertension, smoking and diabetes are classic risk factors, but they are not sufficient to explain the development of atherosclerosis. Inflammatory mechanisms play a key role in all stages of atherosclerosis—from the initial formation of "fatty streaks" to plaque rupture, causing clinical events (i.e., myocardial infarct, stroke, or leg ischaemia (Ross 1999; Lusis 2000). Chronic infections, such as *Chlamydia pneumoniae* infections, have been implicated in the pathogenesis of atherosclerosis as one possible mechanism for induction of inflammation, but these theories remain controversial. (Saikku et al. 1988; Fazio et al. 2009; Vikatmaa et al. 2010). It is not well known why some individuals develop problems in their coronary arteries that lead to myocardial issues; for some patients, the vessels supplying the brain are affected, which causes stroke, while other patients develop walking disturbances or need an amputation due to atherosclerotic changes in their lower extremity arteries. It is also not known why the most important risk factor for coronary disease is hypercholesterolemia, while for stroke it is hypertension, and for lower extremity arteries it is smoking, as each of the three is a risk factor for all three vascular beds. Other sites may also be affected, but the three aforementioned are the most frequent ones. The CAPRIE trial (clopidogrel versus aspirin in patients at risk of ischaemic events) enrolled 19,185 patients with established peripheral arterial disease (PAD), a recent myocardial infarction or recent ischaemic stroke in approximately equal distribution. However, based on the baseline characteristics of these patients, many of them already had a prior history of ischaemic events in more than one vascular bed. Thus, at study entry, ~26% of the patients had ischaemic vascular disease in at least two vascular beds, demonstrating the generalised nature of atherothrombosis (CAPRIE steering committee 1996).

Each year 15 million people worldwide experience an acute stroke of either ischaemic or hemorrhagic aetiology. One third will die secondary to their stroke, while another third experience a permanent disability (Feigin et al. 2009). In Finland, 14,600 persons had a stroke in 2007, and as some suffered a recurrent stroke during the same year, the total annual rate of stroke was 17,100 (Working group appointed by The Finnish Medical Society Duodecim and Finnish Neurological Society, 2011). The incidence of stroke declined from the beginning of 1970 to late 1990 by around 30% in men and by 25% in women. The mortality declined by 60 % in men and by 55% in women during the same time period (Numminen et al. 1996). It has been estimated that if this favourable trend continues, the burden of stroke will not increase substantially in spite of the increasing ratio of elderly people in the Finnish population, but if this development does not continue, there will be over 20,000 first-ever strokes in Finland in 2030 (Sivenius et al. 2009). Atherosclerosis in extra- or intracranial arteries may cause flow disturbances and stroke. 67.3–80.5% of strokes were classified as ischaemic in an overview of population-based epidemiological studies by Feigin et al. (Feigin et al. 2003). Carotid artery stenosis is responsible for 10–16% of all strokes (Poisson and Johnston 2011). 30–40% of ischaemic strokes are preceded by a transient ischaemic attack (TIA), amaurosis fugax (AFX) or a minor stroke, providing a window of opportunity for stroke prevention (Rothwell et al. 2006).

1.2. MANIFESTATIONS OF CAROTID ARTERY ATHEROSCLEROTIC DISEASE

1.2.1. ASYMPTOMATIC ATHEROSCLEROTIC STENOSIS

It is not uncommon that an asymptomatic stenosis of the ICA is found in clinical examination or in the ultrasound examination of the neck. Many neurological symptoms are unspecific, and as the scientific data to support CEA for symptomatic carotid disease is based on RCTs with strict symptom-specific inclusion criteria, the patients with miscellaneous unspecific symptoms should not be classified as symptomatic in the surgical context. Silent infarcts that may be seen in computed tomography (CT) scan or magnetic resonance imaging (MRI), but which have not caused clinical symptoms, should also be classified as asymptomatic in this context. However, it is obvious that patients with such silent lesions will be considered for

CEA by the clinician with special attention (Coccheri 2004; Henriksson et al. 2008).

An asymptomatic atherosclerotic lesion in the carotid bifurcation carries a risk of ipsilateral stroke of 2% or less per year. It has turned out to be difficult to predict which lesions will cause complications and which will remain asymptomatic (MRC Asymptomatic Carotid Surgery Trial (ACST) Collaborative Group 2004; Abbott et al. 2007). The ACSRS (Asymptomatic Carotid Stenosis and Risk of Stroke Study) was a multicentre prospective trial, which stratified the risk of future stroke according to clinical and ultrasound criteria in 1,121 patients with carotid artery stenosis. Grade of stenosis, history of contralateral TIAs or stroke, low echodensity (gray scale media), plaque area and discrete white areas (DWAs) without acoustic shadowing were independent predictors of ipsilateral cerebrovascular or retinal ischaemic (CORI) events (Nicolaides et al. 2010).

1.2.2. WARNING SIGNS: AMAUROSIS FUGAX (AFX), TRANSIENT ISCHAEMIC ATTACK (TIA) AND MINOR STROKE

If a carotid lesion sends an embolus, it may cause different symptoms depending on the artery it occludes. All neurological, potentially ischaemic symptoms should be evaluated on an emergency basis (Lavallée et al. 2007, Rothwell et al. 2007, Luengo-Fernandez et al. 2009).

The ophthalmic artery is the first branch from the ICA, and it is not uncommon that small debris from an ICA lesion to retinal arteries causes an ipsilateral monocular transient ischaemic attack causing visual loss, a phenomenon called amaurosis fugax. Typically, the patient describes total or subtotal transient blindness or a “curtain” in one eye. The attacks are repetitive in nature, and the patients may describe that they have had these symptoms for months or years. Ischaemic blindness may follow from persistent ophthalmic artery occlusion (Benavente et al. 2001; Cohen et al. 2010). In the North American Symptomatic Carotid Endarterectomy Trial (NASCET), the medically treated patients with AFX and a high-grade carotid stenosis had a 16.6% +/- 5.6% (2SD) risk of ipsilateral stroke at 2 years (North American Symptomatic Carotid Endarterectomy Trial Collaborators 1991; Streifler et al. 1995; Mead et al. 2002).

A somewhat larger embolus may find its way to larger intracranial arteries and different areas of the brain and cause either transient or permanent cerebral ischaemia. One way to differentiate a TIA from a minor stroke is that after a TIA, there is no brain tissue death, and brain scanning is negative, whereas a permanent cerebral lesion may be seen after a stroke. As the imaging methods have improved over time and even very small flow disturbances with permanent brain lesion may be seen in advanced imaging, it has become somewhat difficult to distinguish a TIA from a minor stroke (Pavlovic et al. 2010). The most typical TIA symptoms are contralateral limb weakness, which affect the upper limb more severely, contralateral facial palsy and speech disturbances. In NASCET, the 2-year risk of stroke after a hemispheric TIA for patients with a high grade carotid artery stenosis was 43.5% +/- 6.7% (Streifler et al. 1995). Stroke may present soon after a TIA. A half of the strokes that occur within 3 months after a TIA occur within 48 hour from the index TIA (Johnston et al. 2000). Therefore, these symptoms should lead to prompt examinations and treatment (Daffertshofer et al. 2004; Rothwell et al. 2006).

1.2.3. MAJOR STROKE

The first symptom caused by a carotid lesion may be a permanent major stroke leading to severe disability or death. The symptoms and the prognosis of the patient depend on the area and the size of the cerebral infarct. Emergent evaluation and treatment within minutes or hours of symptom onset have proven effective in diminishing the injury and improving the prognosis of the patient (Wardlaw et al. 2009). Early revascularisation may save tissue in the area of ischaemic penumbra (Goldemund and Mikulik 2010). Returning the blood flow to the ischaemic brain cortex causes a potentially dangerous reperfusion injury with a risk of subsequent cerebral haemorrhage. One of the key questions in effective carotid surgery is the timing of the operation after a stroke (Rerkasem and Rothwell 2009a). If the time between the stroke and the operation is too short, and the ischaemic brain area is signifcant, the reperfusion damage may cause further neurological problems or even death. However, sometimes a second or repetitive embolus may cause permanent damage that could have been avoided by early CEA. An acute occlusion of the ICA and potentially salvageable brain tissue can be identified on MRI, and an emergent operation may be justified (Paty et al. 2003, Weis-Müller et al. 2008). However, an acute MCA occlusion is more frequent and intravascular therapies are used more often than emergency surgery in acute MCA occlusion. Intra-arterial mechanical thrombectomy, either alone or combined with thrombolysis, is quite widely used, especially in the USA, although it is not yet supported by RCTs (Alexandrov 2010). The National Institute of Health Stroke Scale (NIHSS) is widely used in clinical trials and daily practice in the evaluation of the severity of acute stroke (Table 1) (Lyden et al. 1994), while the modified Rankin Scale score (mRS) is a widely used method to estimate the outcome of stroke (van Swieten et al. 1988) (Table 2).

Table 1. The National Institute of Health Stroke Scale (NIHSS) used in the estimation of the severity of acute stroke. Modified from Lyden et al. 199

Item	Name	Response
1A	Level of consciousness	0 = Alert 2 = Not alert, obtunded 3 = Unresponsive
1B	Questions	0 = Answers both questions correctly 1 = Answers one question correctly 2 = Answers neither question correctly
1C	Commands	0 = Performs tasks correctly 1 = Performs one task correctly 2 = Performs neither task
2	Gaze	0 = Normal 1 = Partial gaze palsy 2 = Total gaze palsy
3	Visual fields	0 = No visual loss 1 = Partial hemianopsia 2 = Complete hemianopsia 3 = Bilateral hemianopsia
4	Facial palsy	0 = Normal 1 = Minor paralysis 2 = Partial paralysis 3 = Complete paralysis
5	Motor arm (a = left, b = right)	0 = No drift 1 = Drift before 10 seconds 2 = Falls before 10 seconds 3 = No efforts against gravity 4 = No movement
6	Motor leg (a = left, b = right)	0 = No drift 1 = Drift before 5 seconds 2 = Falls before 5 seconds 3 = No efforts against gravity 4 = No movement
7	Ataxia	0 = Absent 1 = One limb 2 = Two limbs
8	Sensory	0 = Normal 1 = Mild loss 2 = Severe loss
9	Language	0 = Normal 1 = Mild aphasia 2 = Severe aphasia 3 = Mute or global aphasia
10	Dysarthria	0 = Normal 1= Mild 2 = Severe
11	Extinction / inattention	0 = Normal 1= Mild 2 = Severe

Table 2. Modified Rankin Scale (mRS) for the estimation of the degree of stroke severity (van Swieten et al. 1988).

Grade	Description
0	No symptoms at all
1	No significant disability despite symptoms: able to carry out all usual duties and activities
2	Slight disability: unable to carry out all previous activities but able to look after own affairs without assistance
3	Moderate disability: requires some help, but able to walk without assistance
4	Moderately severe disability: unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability: bedridden, incontinent, and requiring constant nursing care and attention

1.2.4. CRESCENDO TIA, STROKE IN EVOLUTION, FLOATING THROMBUS AND ACUTE OCCLUSION

Crescendo TIA (TIA attacks occurring with increasing frequency and/or severity) or a stroke with progressing symptoms in an acute setting should be distinguished from a single TIA or minor stroke, as these situations are thought to carry an extremely high risk of recurrent embolism and severe stroke, if left untreated, and they also carry a high risk after CEA (20.2% (CI 12.0–28.4) for stroke in evolution and 11.4% (CI 6.1–16.7) after crescendo TIA) (Rerkasem and Rothwell 2009a). At times, a free-floating thrombus or acute occlusion may be seen at the ICA stenosis, and an emergent operation may be justified after careful consideration (Paty et al. 2003; Bhatti et al. 2007; Weis-Müller et al. 2008).

1.2.5. HYPOPERFUSION AND OCULAR ISCHAEMIC SYNDROME

A severe unilateral or, most often, bilateral carotid and/or vertebral artery stenosis or occlusion may cause hypoperfusion to the brain, especially when the general blood pressure is low or transiently reduced, e.g. in case of severe aortic stenosis, arrhythmias or orthostatic hypotension. The typical complaint is dizziness or syncope, and the patients learn to sit and wait for some time before standing up. If the symptom is severe, CEA or bypass may be justified. However, it has to be remembered that, upon opening the stenosis, the risk of too high a flow (hyperperfusion) to the ischaemic brain is high, and caution in patient selection and perioperative care should therefore be administered (Russell and Gough 2004; Nouraei et al. 2005; Stoneham and Thompson 2009).

OIS is a chronic condition that most commonly results from severe carotid artery stenosis (≥90%), with a 5-year mortality rate of about 40%. Carotid artery stenosis compromises laminar retinal artery flow and results in disturbed flow patterns, hypoperfusion, hypoxia, and ischaemia of highly metabolic retinal tissues. OIS is associated with carotid artery stenosis from 20% to 100% in the reported series (Cohen et al. 2010). However, there is insufficient evidence to draw conclusions about whether surgery is beneficial in these cases or not (Wolintz 2005).

1.3. OTHER DISEASES AFFECTING THE CAROTID ARTERIES

1.3.1. ANEURYSMS

Extracranial carotid arteries are a rare location for aneurysmal disease. Thus, the evidence to support the decision of when to operate is scarce. The feared complication is usually not rupture, but rather embolism and stroke. Occasionally, a large aneurysm may cause symptoms attributable to the compression of the adjacent cranial nerves (e.g. Horner's syndrome) or other compression symptoms like discomfort, pain or dysphagia. It is generally accepted that most aneurysms of the carotid arteries should be considered for surgical or endovascular treatment (Coffin et al. 1997; Hertzer 2000; Attigah et al. 2009). It seems that at least the ICA aneurysms often cause tortuosity that may limit endovascular treatment possibilities. On the other hand, exposure of the high ICA or low common carotid artery (CCA) may be extensive and cause morbidity, and thus steer the decision towards conservative treatment and follow-up (Longo and Kibbe 2005). When feasible, endovascular treatment has a high procedural success rate (Li et al 2009).

1.3.2. TUMOURS

The tissue around the carotid sheath is rich in lymphatic tissue and lymphatic nodes. Therefore, malignant head and neck tumours may either directly infiltrate the carotid artery or send metastatic tumours that grow around the carotid arteries. Paragangliomas of the carotid bifurcation, called carotid body tumours (CBTs), originate from the blood pressure regulating tissue in the carotid bifurcation. CBTs are typically benign but they may occasionally present with malignant characteristics. The carotid body is well supplied with small vessels directly from the carotid artery, and thus the tumours are rich in vasculature and attached to the carotid bifurcation (Boedeker et al. 2005). Malignant head and neck tumour invasion of the carotid arteries may be surgically challenging, and tumours involving the distal ICA are often considered inoperable. Radical tumour excision is, on the other hand, the only curative treatment for malignant neck tumours and may also be considered in selected cases in spite of arterial invasion. Carotid interposition is a method which is in routine use in vascular surgery and which may be performed with minor added morbidity. Therefore, it seems obvious that in some cases carotid artery resection and interposition should be performed instead of taking a risk of incomplete tumour resection (McCready et al. 1989; Wright et al. 1996; Muhm et al. 2002).

1.3.3. FIBROMUSCULAR DYSPLASIA (FMD)

FMD is a rare nonatheromatous arterial disease of unknown aetiology, most commonly affecting the renal or internal carotid arteries. Occasionally, a secondary complication of carotid FMD may lead to embolic neurological events, carotid dissection or aneurysmal dilatation. In addition to antiplatelet therapy, angioplasty of the diseased segment may be indicated. Rare cases of symptomatic complicated carotid artery FMD have been operated by open resection and vein graft interposition (Olin and Sealove 2011).

1.3.4. CAROTID ARTERY DISSECTION

Either spontaneous or traumatic carotid artery dissections are estimated to account for 2% of all ischaemic strokes. However, they account for approximately 20% of strokes in patients less than 45 years of age. A pre-existing atheromatous or, for example, FMD lesion may or may not be identified as the entry site for dissection. Carotid dissection can cause ischaemic stroke either by thromboembolic mechanism or as a result of haemodynamic insufficiency due to severe stenosis or occlusion. Late complications include carotid stenosis with haemodynamic insufficiency and aneurysmal dilatation. Anticoagulation followed by antiplatelet therapy is the most commonly recommended treatment. Most commonly, aneurysms remain asymptomatic and may be followed up, but in rare cases, dilatation may justify open or endovascular repair (Redekop 2008). Both traumatic and spontaneous dissections have been treated with early or late stenting, but there is insufficient evidence to suggest this as a routine treatment (Donas et al. 2008; DuBose et al. 2008).

2. POTENTIAL OF CEA IN STROKE PREVENTION

2.1. INDICATIONS

Prevention remains the best approach to reduce the burden of stroke. Approximately 30–50% of ischaemic strokes are caused by atheroembolism; a large proportion of these are related to atherosclerotic stenosis in the extracranial vessels, and carotid bifurcation in particular (Weimar et al. 2006, Marnane et al. 2010). Approximately 30–40% of patients who suffer a stroke had a preceding transient ischaemic attack (TIA) or minor stroke, which presents an opportunity for prevention (Rothwell et al. 2006). Around 5% of TIA patients presenting to rapid access clinics end up having carotid surgery (Lavallée et al. 2007, Rothwell et al. 2007).

2.2. RANDOMISED CONTROLLED TRIALS

2.2.1. SYMPTOMATIC CAROTID STENOSIS

Symptomatic patients with carotid stenosis were randomised to surgery or medical treatment in three large controlled trials. The Veterans Affairs Study (VA) (Mayberg et al. 1991), the NASCET (North American Symptomatic Endarterectomy Trial Collaborators 1991) and the European Carotid Surgery Trial (ECST) (European Carotid Surgery Trialists' Collaborative Group 1998) delivered level I evidence on the efficacy of CEA in the prevention of stroke in symptomatic patients with 70–99% stenosis of the ipsilateral ICA (Naylor 2006). VA was originally reported in 1991 with a non-significant trend in favour of surgery, but it was stopped early when the initial results of the two larger studies were reported. The final results of NASCET and ECST were reported in 1998.

The data of NASCET and ECST were combined and recalculated by the Carotid Endarterectomy Trialists Collaboration (CETC) (Rothwell et al. 2003), and they showed that medically treated patients with symptomatic high grade (70–99%) ipsilateral ICA stenosis have a 33% risk of suffering any kind of stroke within 5 years, compared with 17% when treated surgically. This estimation gives an absolute risk reduction of 16% in favour of surgery. This means that one stroke could be prevented in five years' time if six operations were performed in this patient group (number needed to treat, NNT = 6), provided that the operative morbidity and mortality is 6% or less. For moderate (50–69%) stenosis, the net benefit was marginal, but significant, with a 4.6% 5-year absolute risk reduction (NNT = 22).

As the combined data included 6,092 patients, with 35,000 patient years of follow-up, several subgroup analyses could be performed. The results have been widely revisited and several international guidelines have been published (Leys et al. 2004; Hobson et al. 2008; Liapis et al. 2009). Subgroups who benefit most from surgery have been identified, and patient characteristics should be taken into account in the decision-making process of clinical practice. On the other hand, it has to be kept in mind that the randomising process was not stratified based on these post hoc subgroup analyses, the validity of which can be questioned.

Over time, the progress in medical management, mainly statins, has presented a major setback for the application of the findings of these trials. Statins were not in use at the time of the trials, and some recent data suggest a significant protective effect of state of the art medical management, especially for patients with carotid stenosis. Some authors have therefore questioned the value of these randomised trials and suggested a more conservative approach towards symptomatic carotid artery disease, at least in moderate risk groups (Amarenco et al. 2006; Sillesen et al. 2008). On the other hand, none of the more recent randomised trials on CEA versus angioplasty and stenting for symptomatic carotid stenosis have yet included a conservative arm.

2.2.2. ASYMPTOMATIC CAROTID STENOSIS

Asymptomatic Carotid Atherosclerosis Study (Executive Committee for the Asymptomatic Carotid Atherosclerosis Study 1995) was published in the United States in 1995 and was followed by a large increase in the number of CEA procedures in the US (Rechtenwald et al. 2007). Fairly similar results could be seen in a larger European Asymptomatic Carotid Surgery Trial (ACST) published much later in 2004 (MRC Asymptomatic Carotid Surgery Trial (ACST) Collaborative Group 2004). Both studies showed a small but significant absolute risk reduction in the risk of stroke at 5 years (5.4–5.9%). The risk of stroke in patients with asymptomatic carotid stenosis is low, only 2% per annum in the ACST, and therefore the rationale for performing CEA on asymptomatic patients is still controversial and requires a very low surgical complication rate. The subgroup most likely to benefit from CEA for asymptomatic stenosis is men under the age of 75.

2.2.3. SURGERY VERSUS ANGIOPLASTY AND STENTING

Surgery is not the only option for treating carotid artery stenosis. As in several other locations, less invasive angioradiological methods have been applied in the carotid territory as well. Carotid angioplasty and stenting (CAS) is widely used for both symptomatic and asymtomatic carotid stenosis treatment, even though scientific evidence supports the use of CAS only in carefully selected cases. A number of randomised studies of various quality have been performed, and several meta-analyses have searched for a definite answer to this question. As with all emerging technology, one major drawback of the randomised studies has been the variability and development in the angioplasty and stenting skills and equipment, and therefore many otherwise well-performed RCTs have been heavily criticised (Eckstein et al. 2008; Mas et al. 2006; Ricotta and Malgor 2008; Ederle et al. 2009a). The most recent meta-analyses, performed after the publication of the so far largest and most comprehensive study, which enrolled symptomatic patients only, the International Carotid Stenting Study (ICSS) (International Carotid Stenting Study investigators 2010), have concluded that surgery is better than CAS (Ederle et al. 2009b; Meier et al. 2010). A corresponding North American study (Carotid Revascularization Endarterectomy versus Stenting Trial, CREST) (Lal and Brott 2009; Brott et al. 2010; Mantese et al. 2010) had great difficulties in recruiting symptomatic patients. The trial was therefore delayed, and ultimately also included asymptomatic patients. The CREST and ICSS showed similar results for symptomatic patients, favouring CEA over CAS. In a pooled analysis of three RCTs on CAS, the patients' age had a significant impact on the treatment effect: in patients <70 years old (median), the 120-day stroke or death risk was 5.8% in CAS and 5.7% in CEA (RR 1.00, 0.68–1.47); in patients 70 years or older, there was an estimated two-fold increase in risk with CAS over CEA (12.0% vs. 5.9%, RR 2.04, 1.48–2.82, interaction $p = 0.0053$) (Bonati et al. 2011). Trials for asymptomatic patients only are underway, but seem to have problems in recruiting patients (Rudarakanchana et al. 2009).

2.3. ISSUES TO CONSIDER IN PATIENT SELECTION

2.3.1. SYMPTOM

The nature of the preceding symptom seems to affect the risk of recurrent stroke. Patients with high grade stenosis who have suffered a stroke or clear hemispheric TIA have a significantly higher risk of a new stroke than patients with transient ocular symptoms, e.g. OR 3.23 (95% CI, 1.47 to 7.12) in NASCET (Streifler et al. 1995). On the other hand, patients with repetitive symptoms have a high risk of stroke (Leira et al. 2004; Gorlitzer et al. 2009). It is controversial whether patient with major strokes and good recovery after acute treatment should be operated emergently, or whether a deferred policy should be applied (McPherson et al. 2001; Bartoli M et al. 2009; Crozier et al. 2011). Major strokes, i.e. infarcts that eliminated useful function in the affected territory, were excluded from NASCET and ECST, and thus there are no large scale randomised data of surgery after major stroke.

However, patients with stroke are considered to have a 2 to 21% risk of recurrent stroke and therefore could be candidates for surgery (Pritz 1997; Crozier et al. 2011).

2.3.2. GRADE OF STENOSIS

The studies of symptomatic stenosis have recognised the grade of the stenosis as the most important predictive factor in the decision-making process. The stenoses have been graded as less than 50% (low grade), 50–69% (moderate) and ≥ 70% (high grade) stenosis. From the CETC data, some quite definite recommendations have been processed (Rothwell et al. 2003). Obviously, several other factors affect the risk of embolisation, but the stenosis grade can be fairly reliably measured, and therefore it is easy to use. However, it has to be remembered that the major RCT data is derived from digital substraction angiographic image data, and today most patients are examined with other modalities prior to surgery.

Soft and irregular plaques with ulceration have been shown to have a greater potential of sending emboli, but despite a vast number of studies, controversy remains about which criteria should be used in the diagnostics (Walker et al. 2002; Rubin et al. 2006; Nicolaides et al. 2010).

2.3.3. OTHER EXTRACRANIAL ARTERIES

Contralateral stenosis or occlusion and stenoses in the vertebral arteries also affect the total cerebral blood supply. If several arteries are severely stenosed, the patients are more likely to have unspecific orthostatic symptoms of dizziness or syncope (Persoon et al. 2009). It has been suggested that a contralateral stenosis or occlusion increases the risk of complications of CEA. In a large trial comparing locoregional anaesthesia (LA) with general anaesthesia (GA) during CEA, the GA group had a higher but not significantly elevated risk of complications in the presence of contralateral occlusion (GALA Trial Collaborative Group 2008).

2.3.4. GENDER

In the pooled CETC data, women carried a higher perioperative risk of stroke. The symptomatic male patients seem to have a higher risk of recurrent stroke and gain more from CEA. The gender difference was also seen in both large trials on asymptomatic patients (Rothwell et al. 2004b, Rothwell and Goldstein 2004). The incidence of stroke is higher in men until the age of 85 (Rosamond et al. 2007). There is a trend towards higher mortality, increased stroke severity, and poorer functional outcome in women. Women are also less likely to have carotid duplex imaging (32.8% vs. 44.0%). Women tend to have more cardioembolic strokes than men and are less likely to have carotid surgery (0.3 vs. 1.5% of all stroke patients) (Di Carlo et al. 2003; Poisson et al. 2010). In a systematic review of 25 studies, women seemed to suffer from a higher perioperative risk of stroke or death (OR 1.31) (Bond et al. 2005). The reasons for these differences are multifactorial and partly unknown, but there are differences in the pathology of symptomatic atherosclerotic plaque, women having a greater frequency of transient endothelial erosion than plaque rupture (Joakimsen et al. 1999, Turtzo and McCullough 2008).

2.3.5. AGE

In the trials randomising symptomatic patients, the older patients benefited more from surgery. In NASCET, patients over 79 were originally excluded, but they were included after the initial reports showed a high benefit in the older group. This is possible due to the fact that as most recurrent strokes are seen within 3 months of the original symptom, the benefits are also seen quite quickly. In the trials for asymptomatic patients, the benefit from surgery may be seen mainly in those patients who live long enough, and thus in both ACST and ACAS (Executive Committee for the Asymptomatic Carotid Atherosclerosis Study 1995) the main group to benefit was those younger than 75 with few comorbidities (Naylor 2006).

3. PROBLEMS IN THE APPLICABILITY OF THE RANDOMISED STUDIES

3.1 DO WE FIND THE CORRECT PATIENTS?

From the point of view of population benefit, the CEA capacity should be addressed to those patients who are most likely to suffer a stroke and who do not have a high perioperative risk. The subgroup analyses of the randomised studies help to identify such patient groups. However, it may still be difficult to find the correct patients from the community for several reasons: the patients may not seek medical attention to their transient symptoms. The medical personnel that is the first to meet the symptomatic patient may not be aware of the treatment possibilities and the need for further neurological evaluation. The imaging studies may not be ordered immediately, but are scheduled as outpatient investigations, and thus delays are inevitable. If the symptomatic patients with a high grade stenosis would be the only ones considered as candidates for CEA, the estimated need for CEA would be around 100-200 / a million inhabitants in the Western countries (Ferris 1998). However, most centres performing CEA also operate on patients with moderate grade (50–69%) stenosis, asymptomatic patients, as well as patients with non-specific symptoms. Thus, in order to treat all the patients who benefit from CEA surgically, the vascular surgical capacity for CEA should be significantly higher.

3.2. INCLUSION AND EXCLUSION CRITERIA

It is very important to understand that if the operation is considered justified by information gained in the randomised studies, the patient should fulfil the inclusion criteria of the trials. The general applicability of the results of a trial decreases if the patient group is very strictly defined. To assess the generalisability of any RCT results, it is necessary to know how many of the potential candidates for CEA were actually included. On the other hand, when the sample size of a trial increases, the possibility to answer a specific question will also increase. However, it will diminish if the inclusion criteria are too loose. Physicians will inevitably meet patients who do not fulfil the inclusion criteria in every day practice, and they will have to extrapolate the trial evidence to be able to treat those patients.

NASCET included 2,885 patients with over 29% stenosis, who had been symptomatic within the preceding 120 days and who did not have significant comorbidities. The enrolment period was from 1987 to 1996, and the follow-up lasted until 1998. Patients over the age of 79 were included only after 1991. Patients were excluded if they had significant organ failure or cancer that was likely to cause death within 5 years or if they had a cardiac valvular or rhythm abnormality. Patients who had uncontrolled hypertension or diabetes or who had experienced unstable angina or myocardial infarction were considered temporarily ineligible. The majority (60%) had had ocular or hemispheric transient ischaemic attacks, and 40% had suffered a stroke, but a major disabling stroke was an exclusion criteria (North American Symptomatic Endarterectomy Trial Collaborators 1991, Barnett et al. 1998). Only one third of the patients operated on in the participating units during the same time period were included in the study. Furthermore, registered national complication rates for all operated patients were higher than those of the patients included in the trials (Wennberg et al. 1998, Bunch and Kresowik 2004).

ECST enrolled 3,024 patients from 1981 to 1994, and the final results were published in 1998. The patients had been symptomatic within the last 6 months. Major disabling strokes were excluded, and 50% of the patients had had a stroke. The others had either ocular or hemispheric TIA. If another, for example a cardiac cause for embolus was present, the patient was not included (European Carotid Surgery Trialists' Collaborative Group 1998).

The ACAS study, published in 1995, included asymptomatic patients with over 60% carotid stenosis who were diagnosed with ultrasound and verified with digital substraction angiography (DSA) imaging if they were randomised to the surgical arm of the trial. The patients were not supposed to have had any related symptoms for the preceding 5 years, and all patients over 79 years of age as well as those with less than a 5-year life expectancy were excluded. They were also not supposed to have had a contralateral ischaemic event within 45 days and not to suffer from a specific disease that could seriously complicate CEA (Executive Committee for the Asymptomatic Carotid Atherosclerosis Study 1995).

ACST included 3,120 patients with unilateral or bilateral carotid artery stenosis of at least 60% on ultrasound and no prior stroke, TIA or other relevant neurological symptoms within the last 6 months. The exclusion criteria were similar to the ACAS, and the patient was not supposed to have any probable source of cardiac emboli or any major life-threatening condition likely to preclude long-term follow-up (MRC Asymptomatic Carotid Surgery Trial (ACST) Collaborative Group 2004).

3.3. DEFINING THE GRADE OF STENOSIS

The NASCET method of measuring the stenosis has been generally accepted and should be used in angiographic diagnostics. In both NASCET and ECST, digital substraction angiography (DSA) was used, and thus the differences in the grading of the stenosis can affect patient selection as the more non-invasive modalities have virtually replaced DSA as the first-line imaging option. Computer tomography angiography (CTA) and magnetic resonance imaging angiography (MRA) are non-invasive modalities, and they are widely used at larger stroke units. In a recent study by Andizei and co-workers, the sensitivity / specificity against DSA for CTA was 95/98% and 93/97% for steady state MRA, far better than for duplex Doppler ultrasound (DD) (sensitivity/specificity was 67/87%) (Andizei et al. 2011). DD is also far more operator-dependent, and no image is stored for later objective comparisons. Another disadvantage of the DD is that it does not show the ICA or intracranial vessels distal to the bifurcation area. The CETC data have been recalculated so that the figures represent the NASCET criteria (Rothwell et al. 2006).

3.4. IMPORTANCE OF REGIONAL CO-OPERATION AND REGIONAL DIFFERENCES

In order to utilise the full stroke prevention power of CEA, a population-based approach should be implemented. All health care professionals should be made aware of the local organisational structure, and guidelines should be written and followed in daily practice. The units where stroke patients are treated should be large enough to have the possibility for immediate vascular imaging. It has been shown that TIA clinics (Lavallée et al. 2007, Rothwell et al. 2007) are effective in stroke prevention and that hospitals with standardised stroke units perform better than general hospitals in stroke outcomes (Meretoja et al. 2010a). Although only about 5% of the patients referred to the TIA clinics will be operated on, the consultation patterns should be emphasised, developed and standardised. The co-operation between primary health care, paramedic personnel, neurologists, radiologists and vascular surgeons should be streamlined to ensure that the patients and their treatment are in focus on a 24/7 basis.

There are major regional differences in stroke prevention and the provision of vascular surgical services. Bunch and co-workers studied CEA processes of care and outcomes in the Medicare population of 10 US states and found considerable state-to-state variation. The 30d combined event rates varied from 4.4% to 10.9% in symptomatic and from 1.4% to 6.0% in asymptomatic patients. They also found significant proportions of patients who were not treated according to the generally accepted guidelines. For example, only 67% of the patients received preoperative (within 24h) antiplatelet therapy although there is strong evidence to support its use. Moreover, 40% of the patients were operated due to a non-specific indication, that is, an indication that was not an asymptomatic stenosis, nor did it fulfil the inclusion criteria for the major RCTs for symptomatic patients. 40% of the operated patients were asymptomatic, and only 20% would have been eligible for NASCET or ECST. (Bunch et al. 2004)

The Finnish National Research and Development Centre for Welfare and Health (STAKES), University hospital districts and the Social Insurance Institution co-operated in a national project to evaluate regional differences in stroke care, the PERFECT stroke project (PERFormance, Effectiveness and Cost of Treatment episodes). Major regional differences were found in the process of care and total costs. In 2003, the percentage of stroke patients who ended up having CEA varied between 0.4% and 3.4% in different regions. It was not possible to explore the reasons for these differences in more detail in the project, but it can be assumed that they are at least partly attributable to the process of care and the implementation of scientific evidence to clinical practice (Meretoja et al. 2010b).

The national vascular register in Sweden, Swedvasc, reports annually the outcome differences of CEA in hospitals throughout Sweden. For CEA in 2009, the rate of "any ipsilateral stroke or mortality" varied between 0.0% (0/98 CEAs) and 20.0% (5/25). If the hospitals with over 50 CEAs/year were the only ones included, the variation would still be between 0.0% (0/98) and 6.8% (4/59), while the total national ipsilateral complication rate was 3.5% (41/1180). Even though the reporting standards may differ between hospitals, it has to be remembered that Swedvasc is a well-validated 20-year old database that is meticulously administered. The differences are similar in Finland, and they may reflect true problems in the processes of care and should therefore be objectively explored (Kantonen et al. 1997; Swedvasc report 2010).

3.5. HOSPITAL RESULTS AND DATA RELIABILITY

Finnish law regulates that treatment episodes must be registered in hospital discharge registries, which are maintained by the government. However, it is not mandatory to report outcome data. Quality control and hospital results are retrieved from separate registries or research projects, which require additional personnel and project funding. The level of reporting is variable due to the lack of standardised national reporting protocols.

Wennberg and co-workers compared the NASCET data to Medicare 30-day mortality data from the same hospitals and also to non-trial hospital data (Wennberg et al. 1998). They found that the trial hospitals had much higher annual procedure volumes, something that has previously been linked to lower complication rates. However, they also found that the crude and adjusted (controlled for age, sex, race, comorbidity and urgency of admission) 30-day mortality rates following carotid endarterectomy differed significantly between the trial data and the Medicare data within the trial hospitals. For example, overall mortality in the trial hospitals (86 hospitals, 6,510 patients) was 1.4% and therefore higher than the NASCET mortality of 0.6% in these hospitals. While the patient characteristics were similar between the trial and non-trial institutions, the trial hospitals had 20% lower death rates. The trial hospitals performed only 6% of the CEAs performed in the US at the same time period. The authors conclude that it should be questioned whether the NASCET results reflect the daily practice, and whether they are applicable to other patients and non-trial hospitals or not.

The available registers are most reliable when only treatment episodes or mortality are concerned. On the other hand, the results of treatment including the outcome of patients should be readily available in order to maintain and improve the quality of care. Input to registers about follow-up data is difficult to obtain, and therefore these quality issues should be addressed within focused administrative and research projects.

4. FACTORS AFFECTING THE RESULT OF SURGERY

4.1. THE ROLE OF DELAY, WHY IT IS IMPORTANT TO ACT URGENTLY

The combined data of ECST and NASCET have been revisited. This data pool shows that the delay between symptom and surgery is a major factor in the effectiveness of CEA. Women with a moderate stenosis benefit in particular if the operation is performed within 2 weeks or one month from the symptom. If the delay is longer than this, then the surgery will be statistically questionable (Rothwell et al. 2004a; Naylor 2006). However, it has to be remembered that the patients were not randomised against the timing of the surgery, but this analysis is a post hoc analysis which is retrospectively extrapolated from the data. Urgent or semi-urgent surgery may increase the risk of perioperative complications, but it still seems that in ECST and NASCET the delay was more dangerous than the increase in perioperative complications, and thus a higher complication rate may be accepted if the delay is short (Naylor 2008). On the other hand, this seems mainly to be true for females and for moderate stenosis, whereas males with high-grade stenosis, which form the most likely group to undergo CEA, can expect good benefits irrespective of whether they are operated early or later after their symptom (Rothwell et al. 2004b).

A meta-analysis and systematic review by Rerkasem and Rothwell in 2009 revealed that the pooled absolute risks of stroke and death after urgent CEA were high in patients with stroke-in-evolution (20.2%) and in patients with crescendo TIA (11.4%). However, there was no significant difference between early and later CEA in neurologically stable patients with recent TIA or non-disabling stroke (neither comparing < 1 week versus ≥ 1 week nor < 2 weeks versus ≥ 2 weeks) (Rerkasem and Rothwell 2009a). Because the risk of recurrent stroke is the highest soon after a minor stroke or TIA, early surgery of stable patients is most likely appropriate.

Urgent treatment and investigation of TIA has been accepted as the best clinical practice in many neurological departments, as it has been established that as many as 17% of the patients with TIA may have a stroke within the first 72h. However, after the first few days quite a few strokes are also seen (Rothwell 2006; Wu et al. 2007; Lasserson 2009). The question remains whether all patients should be operated on within 1–2 days after the first warning sign, and if so, from where the resources to perform these operations would come.

The Early use of eXisting PREventive Strategies for Stroke (EXPRESS) study (Rothwell et al. 2007) was a population-based phase1 versus phase2 study conducted in Oxford, which focused on the effect of early assessment and treatment of TIA or minor stroke on the risk of early recurrent stroke. The main difference between the treatment periods was that the median (IQR) delay to first prescription of treatment fell from 20 (8–53) days to 1 (1–3) day, and at the same time the 90-day risk of recurrent stroke decreased from 10.3% (32/310 patients) to 2.1% (6/281 patients) (adjusted hazard ratio 0.20, 95% CI 0.08–0.49; p=0.0001). However, this effect was probably mainly due to urgent medical treatment as only 5.5% (17/302 in phase 1 and 15/278 in phase 2) of the patients had CEA, and thus the total effect of surgery remains low.

In Paris, a SOS-TIA clinic with 24h access entered 845 TIA patients into a stroke prevention programme between 2003 and 2005 (Lavallée et al. 2007). Forty-three (5.1%) patients had urgent CEA, and 44 (5.2%) patients were treated for atrial fibrillation with anticoagulants. The 90-day stroke rate was low (1.2%) against the ABCD2 score-based estimation of 6.0% (Johnston et al. 2007, Table 8).

The ICSS study randomised 1,713 symptomatic patients to be treated either by CEA or CAS. The investigators reported that only 3 strokes (1.8 ‰) occurred while waiting for the allocated treatment. The median delay from symptom to treatment was 35 days for CAS and 40 days for CEA. On the other hand, the median delay from randomisation to operation was 9 vs. 11 days for CAS and CEA, respectively. Thus, the early strokes which occurred prior to randomisation were probably missed (International Carotid Stenting Study investigators 2010).

In the United Kingdom, only 20% of symptomatic patients had surgery within the two-week target time set by the National Institute of Health and Clinical Excellence (NICE) in 2008 (Halliday et al. 2009). In 2004–2006, only 7% of the Swedvasc operations were performed within 2 weeks (Johansson and Wester 2008). However, the Swedvasc reports from 2009 and 2010 showed that efforts in shortening the delay have been successful and the median time in Sweden had gone down to 12 in 2009 and to 9 days in 2010, but there is still much variation (Swedvasc reports 2010 and 2011).

4.2. HOSPITAL AND SURGEON VOLUME

High volume centres seem to perform better than centres that present low annual number of CEAs (Nazarian et al. 2008; Holt et al. 2007). A meta-analysis performed by Holt and co-workers included 21 studies in a pooled analysis with 885,034 operations from all over the world. Overall, the pooled effect estimate was an odds ratio of 0.78 in favour of surgery at higher volume units, with a critical volume threshold of 79 CEAs per annum. Nazarian et al. presented a rigorous statistical analysis based on 10 years of data from the Maryland hospital discharge register with 22,772 operations. Their study only included in-hospital deaths. They found that high volume centres (>130 CEAs per year) had an odds ratio of 0.945 of death per additional procedure. It seems obvious that an active centralised system allows the systematic improvement of treatment strategies.

Surgeon-specific volume is also an important factor when minimising complications (Kantonen et al. 1998). Different optimal annual numbers have been suggested, but it seems logical that routine and experience improve the results. Cowan and co-workers analysed 35,821 carotid operations from a registry-based National Inpatient Sample in the United States, representing a random representative sample of the whole country (Cowan et al. 2002). They showed that in-hospital mortality, postoperative stroke and prolonged length of stay decreased with increasing number of annual operations per surgeon. They categorised the surgeons into three groups: low volume (<10 procedures/year), medium volume (11-29 CEA/y) and high volume (≥30 CEA/y). Observed mortality graded by surgeon volume was 0.4% for high-volume surgeons, 0.6% for medium-volume surgeons, and 1.1% for low-volume surgeons ($p< 0.001$). The postoperative stroke rate was 1.1% for high-volume surgeons, 1.6% for medium-volume surgeons, and 2.0% for low-volume surgeons ($p < 0.001$). Surgeon speciality had no statistically significant effect on mortality or postoperative stroke. High-volume surgeons performed 51.9% of the operations.

4.3. TECHNICAL ASPECTS AND ANAESTHESIA

4.3.1. PRIMARY CLOSURE VERSUS PATCH ANGIOPLASTY

High-quality evidence supports the use of patch but does not give a definite answer to the choice of graft material (vein vs. synthetic). A Cochrane review from 2004 and an update from 2009 (Bond et al. 2004; Rerkasem and Rothwell 2009b) concerning patch angioplasty versus primary closure included ten trials with 2,157 operations. Patch angioplasty was associated with a reduced risk of ipsilateral stroke during the perioperative period (OR 0.31, 95%, CI 0.15 to 0.63, $p=0.001$) and long-term follow-up (OR 0.32, 95%, CI 0.16 to 0.63, $p=0.001$). Perioperative arterial occlusion was also less frequent in the patch groups (OR 0.18, 95%, CI 0.08 to 0.41, $p<0.0001$), and long-term follow-up restenosis rate was decreased in eight trials (OR 0.24, 95%, CI 0.17 to 0.34, $p<0.0001$). The authors commented that the overall quality of the trials was generally poor and the sample sizes relatively small. The data were not available from all trials, and there was a significant loss to follow-up. Neither long-term nor perioperative deaths were associated with closure groups. The authors concluded that limited evidence suggests that carotid angioplasty may reduce the risk of perioperative arterial occlusion and restenosis. It would also appear to reduce the risk of ipsilateral stroke. Moreover, there is a nonsignificant trend towards a reduction in perioperative any stroke rate and all-cause case fatality

(Rerkasem and Rothwell 2009b). Thus, in the absence of other evidence, it would seem logical to advocate patch angioplasty over primary closure. The choice of graft material seems controversial, and there is not enough evidence to support one material over another. If vein patch closure is used, there are data from observational studies (Riles et al. 1990; Scott et al. 1992; O´Hara et al. 2002) that show a higher rupture rate if the vein is harvested from the ankle. Therefore, if vein material was used, it would seem more appropriate to use the great saphenous vein in the groin.

4.3.2. CONVENTIONAL VERSUS EVERSION ENDARTERECTOMY

Conventional CEA includes a longitudinal incision over the stenosis, endarterectomy and closure either primarily or with patch angioplasty. The distal intimal flaps may or may not be fixated with fine sutures in order to prevent ICA or CCA dissection. Eversion endarterectomy includes a transsection and reimplantation of the proximal ICA. When the transsected ICA is everted and the plaque removed, shunting becomes more difficult or impossible, and the distal intimal flap may not be fixated. Thus, it may sometimes be necessary to convert the eversion technique to longitudinal arteriotomy and patch closure (Brothers 2005; Crawford et al. 2007). A Cochrane analysis from 2001 concluded that eversion CEA can be associated with a low risk of arterial occlusion and restenosis. The reduced restenosis rates did not seem to be associated with either perioperative or late stroke risk (Cao et al. 2004). Thus, according to European Society for Vascular Surgery (ESVS) guidelines, the choice of endarterectomy should depend on the experience and familiarity of the individual surgeon (Liapis et al. 2009).

4.3.3. ROUTINE VERSUS SELECTIVE SHUNTING

Recent European guidelines reviewed the studies from which data on whether to use routine shunting or not could be extrapolated. They found no evidence to support routine shunting during CEA. They also concluded that there is little evidence to support the use of one form of monitoring over another in selecting patients requiring a shunt (Liapis et al. 2009).

4.3.4. ANTEJUGULAR VERSUS RETROJUGULAR APPROACH

The carotid bifurcation is normally approached from an oblique incision following the anterior border of the sternocleidomastoid muscle. Some surgeons prefer to use a more horizontal incision in order to make the scar less visible. Preoperative marking of the bifurcation level with ultrasound may be used in the planning of the incision. The internal jugular vein is the anatomic landmark under the sternocleidomastoid muscle. Either ante- or retrojugular approach may be used. Surgeons preferring the retrojugular approach state that the ICA is easier to mobilise a little higher up, which consequently improves the safety of the operation. The antejugular approach with facial vein ligation is the more traditional one. When choosing the approach, the main concern is cranial nerve injury. One randomised effort to study this has been made in Germany. The study identified more transient cranial nerve injuries (31% vs. 6%, p=0.0014) in the retrojugular approach, which is why the study was aborted early and consequently lost its power. This early postoperative impairment was, however, not statistically significant at the follow-up examination at 6 months (2.4% vs. 0.0%) (Stehr et al. 2008). It still seems that both approaches may be used provided that cranial nerve injury rates remain acceptable (Lutz et al. 2009; Kluk et al. 2009).

4.3.5. GENERAL VERSUS LOCAL ANAESTHESIA

The surgeons who advocate local over general anaesthesia may have a very strong personal opinion as the patients recover faster with less cognitive problems immediately after the operation. It may also be less stressful for the surgeon as he can be sure that the patient will not get new neurological symptoms during carotid clamping. On the other hand, it is logical that local anaesthesia does not protect from embolic complications, and if patient discomfort leads to a need for expediting the operation, it may even be harmful in terms of endarterectomy and patching quality. Recently, a large randomised study was performed in order to find out if one of the anaesthesia methods provided a clinical benefit for the patients (GALA Trial Collaborative Group 2008). The major complication rates in well-performed CEAs are low, and a large sample size of 3,526 operations was consequently included. The GALA trial showed no difference in the primary outcome events (MI, stroke or death 30d post surgery) for the whole patient group, different age groups or high versus low-risk patients. A subgroup of 310 patients with contralateral carotid artery occlusion showed a nonsignificant trend for a smaller complication rate in the local anaesthesia group (8/160 (5.0%) versus 15/150 (10.0%), p for interaction 0.098). The complication rates in the GALA trial were lower than in NASCET and ECST. Other trials were too small to allow reliable conclusions to be drawn (Rerkasem and Rothwell 2009 c). Therefore, it may be concluded that both methods are safe, and patients with contralateral carotid occlusion may benefit from CEA in local anaesthesia.

5. REGISTRIES AND OUTCOME MONITORING

High-quality CEA provision cannot be reached without quality control. Guidelines are based on RCTs whenever possible. However, actual practice is rarely a clean reflection of the RCT setups, and the guidelines may be poorly followed in clinical practice (Holloway et al. 2000; Grol and Grimshaw 2003). Therefore, it is important to know how well actual practice compares with an "ideal situation" of randomised trials. Registries provide a possibility to perform this comparison, and they can be used as valuable quality improvement tools (Schwamm et al. 2006). Implementing a new registry is resource-intensive, and several economical, work force, patient privacy and legislation issues have to be addressed. The annual cost of the Canadian stroke registry was $1 million, and it was still not able to provide a comprehensive nationwide database. This was, however, at least partly due to legislative obstacles: the informed consent required was obtainable only for 51% of the patients (Tu et al. 2004). Meretoja and co-workers calculated that if data entry took 30 minutes per patient, this would increase the work-load by one fully employed person for every 3,000 patients (Meretoja et al. 2010 b).

5.1. DIFFERENT REGISTRY TYPES

Registries may have various interests. Scientific research requires maximal reliability of the data, while health care planning needs maximal coverage. Quality improvement projects should gain information on clinically relevant processes and outcome. Most often, hospital administration or national legislation requires registries on operation and treatment volumes, costs and crude outcome measures like death. These registries are often insufficient to give more detailed data that would be clinically important, including the outcome of patients. Clinical and scientific disease registries address more specific questions for treatment monitoring, quality control and research purposes. National disease or treatment-specific databases have been instituted in several countries for many different purposes. Disease registries often rely upon voluntary inclusion, and the nationwide coverage and allocated resources are variable (Mehta et al. 2002, Meretoja et al. 2010b).

The Scandinavian countries have a long tradition of prospective data collection of all reconstructive vascular procedures. Swedvasc in Sweden, Finnvasc in Finland, Karbase in Denmark and Norkar in Norway have all registered a vast number of patients. The most comprehensive of these is Swedvasc with over 20 years of registered data, continuous data validation and reporting (Swedvasc report 2010).

In addition to a comprehensive annual report, a large number of focused publications have been published from the data. This scientific activity and systematic funding are probably the main reasons for the success of Swedvasc. The Swedish Association of Local Authorities and Regions provides funding for the Registry. Finnvasc, which operated in Finland from 1991 to 1999, was another early register with nationwide coverage. It was the first register in the world to cover the whole country, and it operated on a voluntary basis and with minimal costs (Salenius 1992). Finnvasc could present validated nationwide data during 1991–1995 and variable participation thereafter (Lepäntalo et al. 1994, Kantonen et al. 1997). However, the implementation of a new personal registry law at the turn of the millennium made it impossible for the register to continue. Thereafter, regional registries have continued to gather data. The hospital district of Helsinki and Uusimaa can now present 20 years of registered data for a catchment area of 1.45 million people (Lepäntalo et al. 2008). Karbase (www.karbase.dk) is the Danish vascular registry, which has been collecting data since 1996. Karbase experienced major legislative problems in 2002–2003, when a national indicator project declared many national registers that collected data without a written consent illegal. After strong support from the physicians and local newspapers, the legislation was changed in 2003, and data collection could continue with only some limitations.

5.2. RELIABILITY OF THE REGISTRIES

Perhaps the main concern with all registered data is the reliability of the data. Therefore, regular audits and reports are important in improving the quality of the registries. It is generally accepted that it would be ideal to cross-match different registries kept by different register holders and take advantage of the fact that many patients are included in several different registries (e.g. many vascular patients are included in diabetes and stroke registries). This is seldom possible due to data privacy issues, database differences and different interests of the register holders (Mähönen et al. 2000; Troeng et al. 2008; Meretoja et al. 2010b). Within the PERFECT stroke project, a cross-linked database was established by combining three registers maintained by different register holders (the government, Social Insurance Institution and Statistics Finland). The hospital discharge register, national causes of death register and the national register of prescribed drugs were cross-linked on an individual level with a personal identification number, which is unique for every Finnish citizen. (Meretoja et al. 2010 b)

Modern hospital data systems collect an enormous amount of data. However, the data are often in many different locations, which are not automatically cross-linked. The input may in practice be performed retrospectively by persons who are not involved in the treatment and who do not have background knowledge of the disease or procedures. This can lead to a loss of important data and a loss of reliability. Different private data program providers are often involved, and it is in their interest to keep their own program code a secret. Moreover, hospital data barriers and firewalls are effective and difficult to work around without the data losing its reliability. It is therefore of great importance that these data are validated systematically or at least within research projects (Troeng et al. 2008).

5.3. APPLICATION OF REGISTERED DATA

A registry has its own value only if the data is used to achieve improved patient care. An ideal database would be integrated into hospital patient records, where it could automatically gather the relevant information. The reporting systems should be pre-planned and readily available to make reports that could be used in patient care, health care administration and research. An instant feedback system would also increase the quality of input. In vascular surgery, the Swedvasc database seems to have been able to achieve such a high level with annual reporting and online monitoring (Swedvasc report 2010). Separate focused publications also give more depth to a specific analysis of registered data.

6. SURGERY IN RARE PROBLEMS OF THE CAROTID ARTERY

6.1. SURGICAL ANATOMY AND STANDARD LATERAL EXPOSURE

Carotid and vertebral arteries, which are commonly called extracranial arteries in the neck, secure cerebral blood flow. The carotid and vertebral circulations are united inside the skull as the Circle of Willis, which minimises the risk of cerebral damage even if several of the extracranial arteries should be compromised (AbuRahma and Copeland 1998). Variations in the anatomy of the intracranial arteries and the circle of Willis are common, and only about 25% of individuals have a complete circle of Willis, while variations are less common in the extracranial arteries (Krishnaswamy et al. 2010).

The right CCA arises from the brachiocephalic trunk, emerging normally as the first branch from the aortic arch. On the left side, the CCA typically arises directly from the aortic arch as the second branch. On both sides, the common carotid artery divides into internal and external carotid arteries. The bifurcation of CCA is the area which is exposed in most CEA procedures. In order to expose the most proximal parts of the CCAs, the sternum or clavicle must be divided. The carotid arteries in the neck are reached by following the anterior border of the sternocleidomastoid muscle after the division of the external jugular vein and the platysma. The omohyoid muscle crosses the CCA and is normally left intact. The posterior belly of the digastric muscle, which may be divided without reconstruction in order to gain some extra visibility to the ICA, limits the upper border of the normal exposure. In order to gain access to the higher parts of the ICA close to the skull base, special techniques, which will be described later, must be utilised. The internal jugular vein lies superficial to the CCA and carotid bifurcation. It may be divided but is normally retracted either posteriorly by dividing the facial vein or anteriorly by dividing small veins from the posterior aspect of the internal jugular vein. The superior thyroid artery originates close to the level of the bifurcation either from the CCA or as the first branch from the ECA. The carotid body lies at the cranial aspect of the carotid bifurcation. When operating around the dorsal aspect of the CCA and ICA, care should be taken as the vagal nerve runs parallel to these arteries, often within the carotid sheath. The superior laryngeal nerve, a branch from the vagal nerve, lies deep in the superior thyroid artery and the ECA. The hypoglossal nerve runs across the ICA cranial to (or seldom at) the level of the bifurcation. The glossopharyngeal nerve runs in a similar way cranial to the hypoglossal nerve and is normally protected by the styloid process. The most superficial segment of the accessory nerve most often lies in a triangle formed by the posterior belly of the digastric muscle, internal jugular vein and sternocleidomastoid muscle (Cavalcanti et al. 2010). The mandibular branch of the facial nerve must also be avoided as it may lie caudal to the parotid gland and be damaged, most often by careless use of retractors (Lutz et al. 2009).

6.2. EXTENDED EXPOSURE TECHNIQUES

In order to expose the internal carotid artery closer to the skull base, modifications to the standard operation technique are needed (Beretta et al. 2006). Mandibular subluxation allows more space for the operation, and it is accompanied by styloid process resection, which is intended to expose the ICA at the level of the glossopharyngeal nerve (Dossa et al. 1990). Lateral mandibular osteotomy techniques have been used for higher exposure, and vertical osteotomy of the mandibular ramus was introduced in this context by Larsen et al. to make better use of physiological muscle pull. However, these lateral techniques are limited by the bony structures of the skull base (Batzdorf and Gregorius 1983; Mock et al. 1991; Larsen et al. 1992). Petrous bone drilling and cervical-to-petrous carotid artery bypass techniques have been used in order to gain exposure to the ICA within the bony canal (Alimi et al. 1996, Eliason et al. 2002; Malikov et al. 2010).

AIMS OF THE PRESENT STUDY

1. To define the theoretical potential efficacy and need of carotid surgery in stroke prevention in different populations.

2. To validate the reliability of registered data on carotid surgery and its complications.

3. To compare registry-based data on CEA and its complications from different countries.

4. To explore the referral pathways and reasons for delays from symptom to CEA in the Helsinki region and to suggest ways to improve patient flow.

5. To review and discuss the opportunities beyond standard carotid operations in tumour and aneurysm surgery and to present a novel multidisciplinary approach to operate the internal carotid artery close to the base of the skull.

MATERIALS AND METHODS

In order to address the question of how to organise carotid surgery effectively, we wanted to study different quality issues. First we wanted to evaluate the potential of carotid surgery in stroke prevention. We compared the published data from Oxford to the numbers of Helsinki university district and the Sohag governance. The main idea was to see how close to the optimal theoretical effect HUCH can perform and what potential total effect might be expected if the ideal stroke preventive carotid surgery would be implemented in Upper Egypt, where almost no CEAs were performed at the time of the study. We chose to suggest surgery for symptomatic high-grade stenosis only in cases where the estimated NNT to prevent one stroke in five years was ca. 6, and assumed that other criteria derived from the RCT data can be accomplished. First we compared the population structures and TIA and stroke incidences in the three areas. The incidences of TIA and first-ever ischaemic stroke in Upper Egypt were derived from a community-based door-to-door survey of 25,000 people performed in the Sohag governance (Kandil et al. 2006). The corresponding rates in Southern Finland were the average rates from four Finnish stroke epidemiological studies in three different regions in Finland (Aho 1975; Sivenius 1982; Kotila 1986; Rissanen 1992), whereas those of Wessex were based on the published data of the Oxford Community Stroke Project (Bamford et al. 1988; Dennis et al. 1989; Ferris et al. 1998). To estimate the proportions of symptomatic patients with operable high-grade carotid stenosis we used published data on incidence (Rothwell et al. 2006). The current actual levels of CEA provision were derived from local registered data in Finland and Egypt and from published data from Oxford. The estimated needs of CEA and the actual/need ratio were reported.

After defining the theoretical impact of surgery for high-grade symptomatic stenosis, we wanted to evaluate how well our clinical results compared to the results in randomised studies and how reliable the registered data that is used in clinical practice and planning was. We retrieved all CEA operations performed during 2000–2005 from two different register sources and cross-matched the individual patients according to their personal identity number. The Department of Vascular Surgery in HUCH has two different registries in use for collecting patient clinical data: the local vascular registry, called HUSVASC, which is supported and funded by the hospital district of Helsinki and Uusimaa, and the governmental nationwide hospital discharge registry (HDR) called HoitoILMOitusrekisteri HILMO, which at the time of the study was maintained by the National Research and Development Centre for Welfare and Health (STAKES), Finland.

HUSVASC was mainly designed to collect data of vascular surgical interest of any patient with arterial disease, treated either surgically or endovascularly. HUS-

VASC also includes the patients in the region previously included in the earlier nationwide vascular registry, Finnvasc (Salenius 1992, Lepäntalo et al. 1994). Since 1967, all operative codes and treatment episodes in Finland have been recorded in the Finnish HDR (Mähönen et al. 1997). To identify CEA operations from HUSVASC, a quite liberal search policy can be used. For example, operative anatomy, indication of operation (stroke, transient ischaemic attacks, amaurosis fugax, and asymptomatic stenosis) or the related operative codes may be used. To extract data from the HDR a more restricted search policy is mandatory. The nationwide operative codes used both in HUSVASC and HDR were retrieved from NOMESCO (Nordic-Medico-Statistical Committee) Classification of Surgical Procedures (NCSP) (www.helsedirektoratet.no) including codes for thrombendarterectomy (PAF), patch angioplasty (PAN), and graft interposition (PAH) of the internal (14), external (13), or common carotid arteries (12). We used combined search criteria to track any missing CEAs in the period from 2000 to 2005. We assumed that this combined search tracked all CEAs. All inconsistent data were crosschecked against patient records. Incorrect inclusions, such as carotid area bypasses, were discarded manually. To find all the incorrectly coded CEAs, we searched HILMO for any surgical or endovascular intervention to the aortic arch and its branches in the same period. The results of CEA from both registries were validated and crossmatched against each other at different levels. After identification, all deficient or faulty registrations in HUSVASC were corrected, but we had no access to correct any false data in the HDR. To assess the ability of the different registries to give comparable rates of morbidity and mortality, we searched both registries for the prospectively collected major strokes and fatal events within 30 days after CEA. Results were stratified according to the indication of the operation and compared to those from the completed HUSVASC dataset. Specific codes for postoperative complications (ICD-9 code 997.x and ICD-10 codes Y65, Y69, Y83, and Y88.x) were also searched. In order to specify how well a simple search of CEAs (codes PAN14 for patch angioplasty and PAF 14 for endarterectomy of the internal carotid artery, normally used for carotid bifurcation endarterectomy as well) would catch the operations, we also compared this simplified search with the ones described above. Finally, the perioperative morbidity and mortality figures retrieved from the two different registries were compared against each other in order to analyse whether systematic escape of data was present and whether it would lead to severe problems in the reliability of the results in any of the registries or not.

Further, in order to analyse patient referral pathways and the time from symptom to surgery critically, we identified 100 consecutive symptomatic CEA patients operated at HUCH. After approval by the local ethics committee, a retrospective data collection of a cohort of 100 consecutive symptomatic patients planned for CEA was begun from the day of approval, and the patient records were revisited. Data collection included 14 months from August 2007 to October 2008. The medical history data were collected from the HUSVASC registry, and additional data from medical records were added if the registry data were insufficient. During the study period, the national recommendations stated that CEA should be performed as soon as possible from the index symptom, preferably within 2 weeks (Working group appointed by The Finnish Medical Society Duodecim and Finnish Neurological Society, Update 2011).

We categorised different steps of delay to find out where improvements should be made. The time from symptom onset, the pathway of reaching vascular surgery consultation, rate-limiting steps and the delays before surgery were defined. We categorised the delay as: patient-related (the time from the symptom to the first health care provider contact); referral delay (the time from the general practitioner or private physician referral to the first meeting with a neurologist); neurological delay (the time from meeting the first neurologist to the consultation of a vascular surgeon); radiological delay (the time from the referral to imaging to the execution of the imaging) and surgical delay (the time from the first surgical consultation to CEA). These delays overlapped, and their sum was therefore greater than the total symptom to knife time (SKT, i.e. the time from the index symptom to CEA). After the patient-specific delays had been registered, the data published by the CETC (Rothwell et al. 2003, Rothwell and Goldstein 2004, Naylor 2006) were used as a reference together with sex and grade of stenosis, and an NNT number for each patient could be calculated. The NNT figures could then be used to estimate the effectiveness of vascular surgery provision in our practice. The patterns of delay could also be used to suggest which actions should be undertaken to reduce delays.

Together with the VASCUNET Steering Committee we also compared registered data from several different countries. VASCUNET is a joint venture of European vascular registries including data from Australia and New Zealand. The VASCUNET is administered and funded by ESVS. In this comparison, it was not possible to cross-match patient populations. However, we were able to compare the registered surgical praxis in different countries and to analyse the theoretical impact of CEA in different countries and regions. We had access to data from 53,077 carotid procedures from seven national (Denmark, Hungary, Italy, Norway, Sweden, Switzerland and the United Kingdom) and two regional vascular registries (Australia and Finland) with somewhat variable input of data (Table 2). The data were analysed overall and per country. The main focus was to compare the data from the nine countries considering patient demographics, comorbidities, indications, operative data, outcome and effectiveness. CAS was not included in the outcome analysis. In the outcome analysis, the data were first divided into symptomatic and asymptomatic patients.

The data were then further divided into three categories of effectiveness according to the published data from randomised studies (Rothwell et al. 2004a; Naylor 2006): 1. highly effective including all symptomatic men with carotid stenosis

≥ 50% and symptomatic women ≥75 years of age with carotid artery stenosis ≥ 50%; 2. moderately effective including symptomatic and asymptomatic women <75 years of age with stenosis ≥ 50% and asymptomatic men with stenosis ≥ 50%; 3. not effective including all patients with stenosis <50% and females ≥ 75 years with any asymptomatic stenosis (Table 4). In order to demonstrate the effectiveness, a crude number of strokes prevented per 1,000 operations was calculated for each group: they were 150, 75 and 0 for groups 1, 2 and 3, respectively. The figures were estimated from calculations performed from the pooled analysis of the major RCTs (Rothwell et al. 2003; Rothwell and Goldstein 2004; Naylor 2006).

Table 3. Carotid procedures included in the Vascunet dataset (IV).

	2005	2006	2007	2008	2009-10*						
	N	N	N	N	N	Total N	Inv. data%	CAS%	Asympt.%	Population	% pop. incl.
Australia	528	494	468	543	469	2502	0.0	11.7	33.1	21.5	23.2
Denmark	288	334	346	402	459	1829	0.0	0.1	0.0	5.4	100
Finland	144	136	195	237	264	976	0.0	3.3	15.6	5.4	33.5
Hungary	3	1	1	647	656	1407	7.0	3.4	46.1	10.0	78.2
Italy	0	0	8137	7559	5653	21349	0.0	17.4	68.6	60.4	100
Norway	314	354	370	359	0	1397	0.0	2.9	20.5	4.7	100
Sweden	965	1116	1021	1183	1175	5465	0.1	6.8	22.8	9.4	93.4
Swizerland	424	453	484	465	0	1826	0.0	0.5	40.4	7.8	100
United Kingdom	235	2912	2764	4113	6116	16326	1.1	0.6	16.8	62.3	100
Total	2901	5800	13786	15508	13263	53077	0.5	8.7	40.1	186.9	83.7

CAS=Carotid artery stenting

* = Includes numbers from year 2010 in the data from Unided Kingdom (1521 CEAs and 4 CASs) and Hungary (4 CEAs)

Inv. data% = Invalid data, percentage of false inputs that could not be used in the analysis (e.g. year irrelevant)

Asympt.% = Proportion of asymtomatic patients

Population = population in millions

% pop. incl. = Percentage of the population included in the registered data

Table 4. Grouping of patients in three effectiveness categories

Group	Strokes prevented /1000 operations	Patients included
1	150	Symptomatic men with ≥ 50% stenosis Symptomatic ≥ 75 year old women with ≥ 50% stenosis
2	75	Symtomatic < 75 year old women with ≥ 50% stenosis Asymtomatic men with ≥ 50% stenosis Asymptomatic < 75 year old women with ≥ 50% stenosis
3	0	Any patient with stenosis < 50% Asymptomatic ≥ 75 year old women

Finally, to study the surgical limits of carotid surgery we present a case series of five patients operated on with a special midline mandibulotomy technique combined with neck incision. The technique was developed by our team of vascular surgeons, maxillofacial surgeons and ear, nose and throat specialists. We also reviewed the world literature on different surgical techniques that have been suggested in the treatment of problems related to the internal carotid artery close to the skull base beyond routine carotid exposure.

STATISTICAL ANALYSES

In studies I, II and V, simple calculations and estimations were used. In studies III and IV, distributions of the continuous variables were studied and tested for normality. A univariate comparison between the groups was performed with Student's t test or Mann-Whitney Rank Sum test for continuous variables, and with Pearson $\chi2$ test for discrete variables. Two-sided values of $P<0.05$ were considered significant. For multivariate analysis testing associations a model of binary logistic regression analysis including potential confounders as identified by univariate analysis ($P\leq0.20$) was applied. All statistical analyses used SPSS 17.0 (SPSS Inc., Chicago, IL).

RESULTS

ESTIMATED NEED AND ACTUAL PROVISION OF EFFECTIVE CAROTID SURGERY FOR STROKE PREVENTION (I)

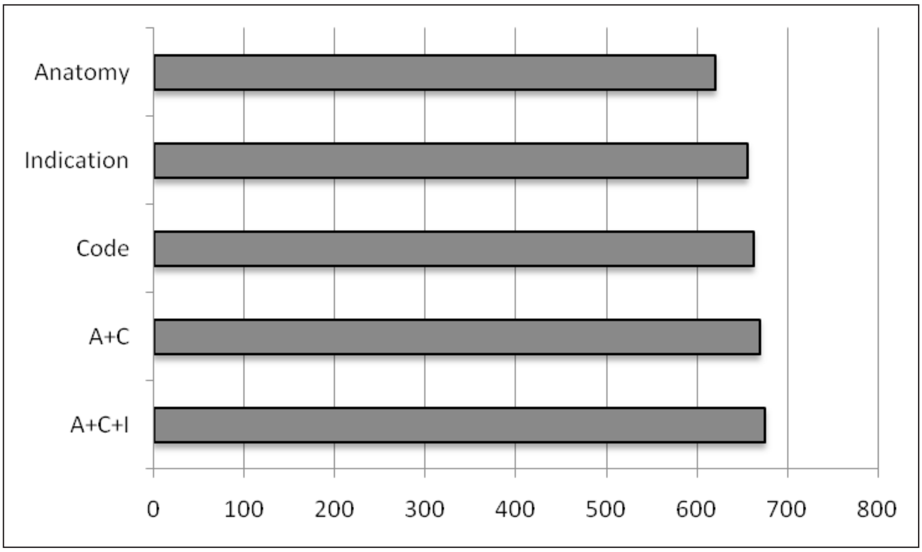
The age structures and population pyramids from the UK, Finland and Egypt showed that the Egyptian population is significantly younger, while the aging of the population is faster in Finland and UK. The percentage of the population aged 65 years or older was 16% and 15% for the British and the Finnish populations, respectively, but only 4% for the Egyptian population. According to the incidence of TIA and stroke and the population data of the three regions, the annual number of symptomatic (TIA or stroke) patients with ipsilateral 70–99% ICA stenosis could be estimated in each region. According to the estimations, there is a gap between the estimated need and actual provision in all three areas. Based on the published data, there are at least 1,650 symptomatic patients with severe ICA stenosis who would be eligible for effective CEA in Upper Egypt each year, compared with 427 and 239 patients in Wessex, UK, and Uusimaa, Finland, respectively. Assuming that in one year, all 1,650 patients could be found and operated on in Upper Egypt with a 6% complication rate, 275 strokes could be prevented (assuming an NNT of 6). The corresponding figure in the HUCH region is 40 prevented strokes and 71 in Wessex. The actual number of CEAs per year was about one half of the estimated need in Wessex and Uusimaa but much lower in Upper Egypt.

RELIABILITY OF REGISTERED DATA (II,IV)

The search engine in HUSVASC provides a possibility to search information with several different parameters and to combine them quite liberally. Searching HUSVASC for CEAs offered a different result with each preplanned search within the same time range (2000 to 2005), showing that different data parameters are not equally reliable, and thus none of them should be used alone. The greatest number of CEAs (HUSVASC-initial, n = 675) was obtained using these combined criteria (Figure 1). Out of these, 518 (71%) were endarterectomies and 118 (23%) were CEAs with patch angioplasty of the ICA, while the remaining 39 (6%) were interposition grafts from the internal or common carotid arteries, thrombendarterectomy of the external or common carotid arteries or incorrectly coded or uncoded operations.

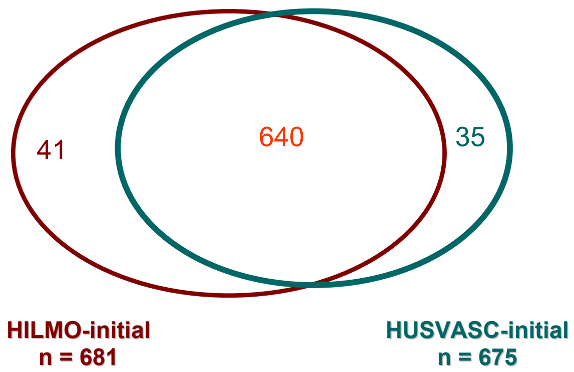
ICD-10 Codes PAF 12-14, PAN 12-14 and PAH 12-14 were used in the HILMO search to create a dataset that would not miss CEAs even if they were miscoded.

Figure 1. Number of CEAs retrieved from HUSVASC registry in the years 2000–2005 using variable search criteria. Different searches yielded different numbers of patients due to incomplete data and miscoding. The most comprehensive search used a combination of codes, but this also included operations that were not intended to be included (e.g. by-passes). A = Anatomy, C = Operative code (NOMESCO), I = Indication. (II)



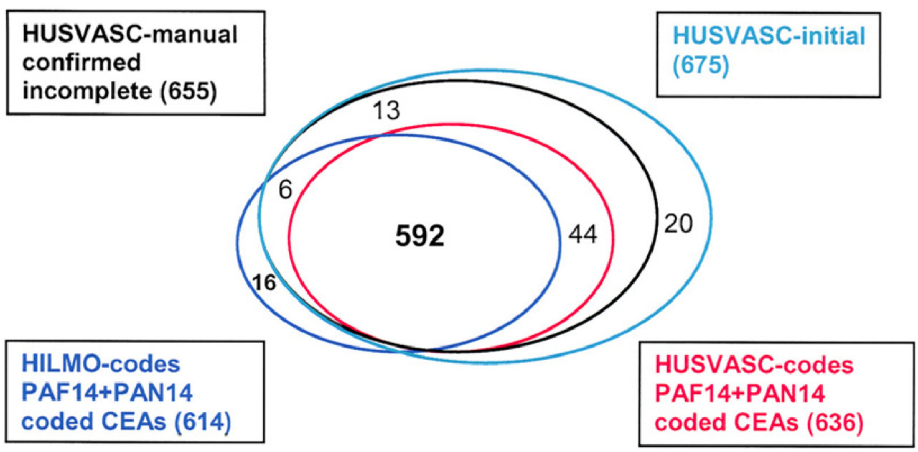
Cross-matching these initial results from the two datasets (681 in HILMO against 675 in HUSVASC) showed that 640 CEAs were registered in both; 35 were only included in HUSVASC, while 41 were only recorded in HILMO (Figure 2). To determine the reasons for missing these "assumed" CEAs from HUSVASC, we checked the patient records. Out of the 41 operations, 12 (29%) were not CEA operations, 10 (24%) were registered but without any medical data, 6 (15%) were entirely unregistered, 6 (15%) were missing some key data such as anatomy or the indication for the operation, 2 (5%) had incorrect operative codes, and in the remaining 5 cases we could not identify any reason.

Figure 2. Comparison of the initial searches showed that 640 patients were included in the search from both datasets. 41 were only included in HILMO and 35 only in Husvasc (II).



When the operative codes PAF14 and PAN14, which are the two most specific codes for CEA, were used, the majority of the initial CEA results in both datasets were included (94% for HUSVASC and 90% for HILMO). Cross-matching the 636 operations coded as PAF14 or PAN14 in HUSVASC (HUSVASC codes) against the corresponding 614 in HILMO (HILMO codes) showed that 592 operations were available in both sets: 44 only in HUSVASC and 22 only in HILMO (Figure 3).

Figure 3. Multilevel cross-matching based on individual personal identity codes revealed several problems in the datasets, and only 592 patients were retrieved with all search strategies (II).



According to the final dataset, the perioperative mortality, morbidity, and combined morbidity and mortality rates were 0.5%, 2.2%, and 2.7%, respectively. Stratification of these results by indication for surgery showed that stroke patients had the highest rates of morbidity and combined morbidity and mortality (3.2% and 3.9%, respectively). The rates for TIA patients (both 1.8%) and amaurosis fugax patients (morbidity and combined morbidity and mortality rates of 1.8% and 2.3%, respectively) were lower. None of the asymptomatic patients suffered a perioperative stroke or death. Furthermore, both registries, irrespective of the completeness of the data, provided comparable rates of morbidity and combined morbidity and mortality. Yet, stratification of these rates according to the indication of operation showed greater differences between datasets, particularly for stroke rates. A search using codes for postoperative central nervous system complications available in the ICD coding systems (ICD-9 code 997.x and ICD-10 codesY65, Y69, Y83, and Y88.x) in the entire registry of HUCH yielded 38 patients, but none of them had undergone CEA.

DELAY AND PATIENT REFERRAL PATHWAYS IN HELSINKI AND UUSIMAA (III)

As planned, 100 consecutive symptomatic CEA patients were identified. During the same time period, 42 asymptomatic patients were operated (26.9%), and 10 symptomatic patients were treated with CAS, but they were excluded from the analysis. The first contact with a health care professional is presented in Table 5.

Table 5. The first health care professional contact of the 100 patients operated in HUCH (III).

First health care system contact (N)	
Health care centre	43
Secondary referral centres	14
Neurologist HUCH	14
Ophthalmologist	7
Private practitioner	6
Internal medicine	6
Neurologist outside HUCH	5
Surgical ward	4
Pain clinic	1

Thirty-two percent of the patients were operated within 4 weeks and eleven percent within two weeks of their presenting symptom. It was more likely that CEA was performed within two weeks if an emergent consultation to the tertiary clinic hospital neurologist on-call took place (OR 12.6, 95% CI 1.5–104, p=0.019). The same was true for having the operation within one month with an OR of 6.1 (95%CI 2.4–15.8; p<0.0001). Overall, about a half of the patients had emergency consultation or referral (47.0%; 47/100).

The median time from the index symptom to surgery was 47 days (3–688 d). The total delay was significantly shorter if the index symptom was a minor stroke with a median of 34 d, (range 7–216 d) or a major stroke (median 22 d; range 8–102 d) compared to amaurosis fugax (median 66 d; range 9–688 d) or TIA (median 69 d; range 3–216 d) (p<0.005, Kruskall-Wallis).

If the vascular surgeon was consulted during the first visit, the median total delay was 25 d (range 3–148 d) versus 84 days when the vascular surgeon was not consulted (range 10–688 d; p<0.0001). Moreover, if the carotid examinations were performed during the first hospitalisation, the total delay was significantly shorter compared to elective carotid artery examinations: median 29 d (range 5–148 d) vs. 89 d (range 21–688 d); p<0.0001.

During the delay from the first symptom to surgery, 10 (10%) patients had recurrence or progression in their symptoms, i.e. recurrent TIA (n=2), progression of TIA to minor stroke (n=2), progression of minor stroke symptoms (n=2), progression of symptoms from minor to major stroke (n=2) or progression of major stroke (n=2). All these patients underwent CEA, and the median (range) total delay from symptom to surgery for these patients was 8.5 (1–30) days. When compared to the data of the subgroup analysis from the randomised studies (Naylor 2006), 62 (62%) of the patients were operated with a good benefit expectation (NNT<7), 19 (19%) with a reasonable benefit expectation (NNT 8–20) and 19 (19%) were operated too late (Table 6).

Table 6. All 100 CEA patients grouped according to their sex, severity of stenosis and time to surgery from index symptom, and the respective theoretical number needed to treat derived from the NASCET and ECST subgroup data[6,9]. The colours represent different NNT groups. Green: NNT < 7 equivalent to best possible benefit; Yellow: NNT = 8–20 equals to reasonable benefit; Red: operation theoretically harmful for the patient (i.e. NNT cannot be calculated). The number represents the number of patients in each group. (III)

Degree of stenosis / gender	0-2 weeks	2-4 weeks	4-12 weeks	> 12weeks
70-99% male	8	11	19	16
70-99% female	3	4	10	6
50-69% male	0	5	7	8
50-69% female	0	1	2	0

There were 2 perioperative major strokes and 1 minor stroke. These operations took place 9 and 52 days from the index symptom, respectively. One further patient, operated 102 days from a TIA, died on the 4th postoperative day. She had postoperative headache, a generalised seizure and high blood pressure postoperatively, but the transcranial Doppler (TCD) finding and clinical picture were otherwise untypical for hyperperfusion syndrome. In autopsy, the cause of death was cerebral anoxia, and the operated area was smooth with no residual flaps. Moreover, there was 1 hyperperfusion syndrome, 1 TIA and 3 cranial nerve injuries. Taken together, the rate of disabling stroke and mortality was 3/100 (3%) and the rate of any stroke or death 4/100 (4%).

INTERNATIONAL REGISTRY DATA COMPARING EFFECTIVENESS OF CEA IN NINE COUNTRIES (IV)

Of the 53,077 carotid procedures, 48,185 were CEAs, 4,602 were CASs and 290 were invalid data with unrelated years recorded, i.e. false data input. Finland and Australia presented regional register data covering 33.5% and 23.2% of the total population, respectively. The other countries presented national data with a 78.5–100% coverage.

Table 7. Effectiveness of carotid provision in the whole study population, based on the effectiveness categories defined in Table 4. Utility rates of carotid territory intervention (CAS+CEA) in one year. Year 2008 was chosen because it represented the most comprehensive data from all countries (IV).

	SPrev/1000	PEff %	Sympt %		2008 N	Utility rate	Utility S
Australia	106	81.4	66.9		543	10.9	7.3
Denmark	131	100	100		402	7.4	7.4
Finland	120	91.6	84.4		237	13.2	11.1
Hungary	87	66.7	53.9		647	8.3	4.7
Italy	73	55.7	31.4		7559	12.5	3.9
Norway	116	88.7	79.5		359	7.7	6.1
Sweden	117	89.5	77.2		1183	13.5	10.4
Switzerland	102	78.1	59.6		465	6.0	3.6
United Kingdom	118	90.4	83.2		4113	6.6	5.5
Total (N or average)	100	76.5	70.7		15508	9.6	6.7

SPrev / 1000 = Estimated number of strokes prevented in 5 year follow-up by performing 1000 CEAs

PEff % = Proportional effectiveness, the most effective country (Denmark) used as a reference

Sympt % = Proportion of symptomatic patients

2008 N = number of operations in 2008

Utility rate = number of carotid interventions / 100,000 inhabitants in 2008

Utility S = number of carotid interventions for symptomatic disease / 100,000 inhabitants in 2008

Each patient was categorised into a theoretical effectiveness category according to Table 4. Based on this assumption, different values for comparison could be calculated. The numbers of strokes prevented per 1,000 operations (in the 5 year follow-up) was 131 in Denmark and 73 in Italy; it can therefore be estimated that with these assumptions, the CEA provision in Italy reaches 56% of the effectiveness in Denmark (Table 7 and Figure 4).

The utility rate of the representative year 2008 gave 6.0 to 13.5 operations per 100,000 inhabitants in the included area, the lowest in Switzerland and the highest in Sweden. If symptomatic patients had only been operated, the corresponding utility rate would have varied between 3.6 in Switzerland and 11.1 in Finland (Table 7).

The combined mortality and stroke figures show that CEA for asymptomatic lesions was safer in all countries apart from Finland. However, the small difference in Finland is not significant. The reported complication figures stratified by symptom and admission mode are presented in Table 8.

Figure 4. The proportional effectiveness of carotid provision divided into three levels for each country.

1. (HIGHLY EFFECTIVE): ≥50% stenosis in symptomatic men, ≥50% stenosis in symptomatic females ≥75 years old

2. (MODERATELY EFFECTIVE): ≥50% stenosis in asymptomatic men, ≥50% stenosis in symptomatic and asymptomatic females < 75 years old

3. (MILDLY OR NOT EFFECTIVE): <50% stenosis, asymptomatic stenosis in females ≥75 years

D.m. = data missing

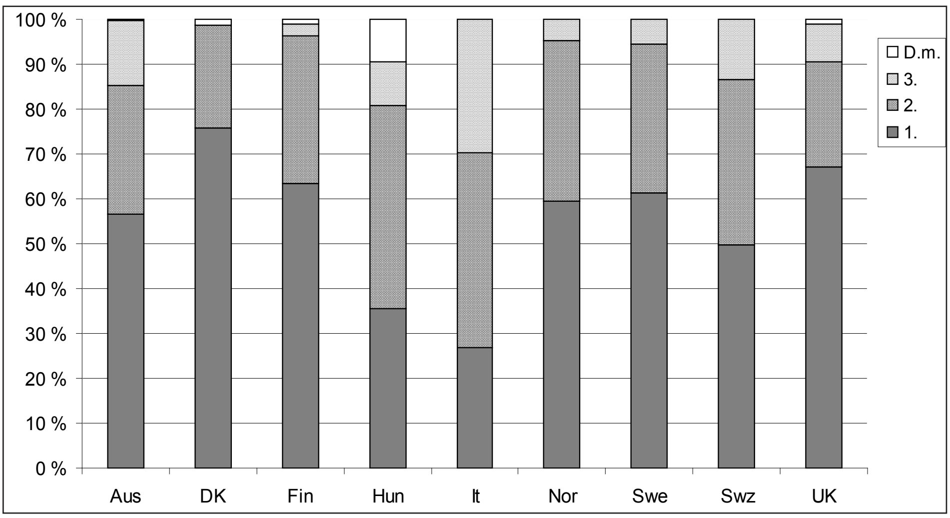


Table 8. Death and/or stroke rate in asymptomatic and symptomatic carotid endarterectomy patients (IV).

	Asymptomatic	Symptomatic		
	M+M %	M+M %	Emergency	Elective
Australia	0.9	2.1	3.1	1.5
Denmark	N.a.	3.7	6.0	3.6
Finland	2.0	1.9	3.0	1.8
Hungary	2.1	3.4	4.1	3.3
Italy	0.5	0.9	3.8	0.7
Norway	2.5	3.8	7.0	3.6
Sweden	2.7	3.0	3.5	2.5
Switzerland	1.6	3.4	D.m.	D.m.
United Kingdom	1.8	2.4	3.6	2.3
Total	1.0	2.4	3.6	2.1

M+M = Morbidity and mortality, i.e. combined stroke and death
D.m. = data missing

The binary logistic regression model included all 53,077 cases. The symptomatic patients had a higher risk of stroke or death than asymptomatic patients (OR 1.37, 95% CI 1.14–1.63, p=0.001). CAS was more dangerous than CEA (OR 1.78, 95% CI 1.36–2.33, p=0.000), and emergency operations had more complications than the elective ones (OR 2.04, 95% CI 1.68–2.49, p= 0.000). From the whole material, not taking into account the proportion of different indications (symptomatic or asymptomatic), the theoretical effectiveness or the reliability of the inclusion of complications, it seemed safest to undergo CEA in Italy and most dangerous in Norway with OR of 0.26 (95% CI 0.21–0.33, p= 0.000) and 2.02 (95% CI 1.49–2.72, p = 0.000) respectively. The United Kingdom was used as a reference.

EXTENSIVE CAROTID SURGERY AND MIDLINE MANDIBULOTOMY (V)

Five patients were operated on using combined midline mandibulotomy and extended neck incision for medial carotid exposure. Two patients had high internal carotid aneurysms extending close to the skull base. Three patients had a neoplastic lesion: 2 malignant oral tumours with neck metastasis and 1 primary paraganglioma. All operations were initially successful, and no immediate strokes or deaths were encountered. One aneurysm patient and the paraganglioma patient had almost no disease or operation-related morbidity at follow-up. One patient with an extended lingual epidermoid carcinoma with local extension into the mandibular bone was recurrence-free at 3.6 years. One aneurysm patient with glossopharyngeal nerve injury died 30 days postoperatively due to aspiration pneumonia. Another patient died due to malignant tumour recurrence after 15 months. Hypoglossal and glossopharyngeal nerve injury was also seen in the patient with a paraganglioma invading the glossopharyngeal nerve close to the cranial base, but the patient recovered and returned to his previous activities. The vagal nerve was resected in all three tumour cases with minimal morbidity. The external carotid artery was reconstructed end-to-side with the interposition graft in two cases and ligated in three cases. Median operation time and blood loss were 550 minutes (148–705 minutes) and 1,730 mL (1,000-3,500 mL), respectively. A Pruitt-Inahara shunt was used in 3 patients with carotid closure time of 8–11 minutes. The carotid closure time was 15 and 31 minutes in the aneurysm operations in which no shunt was used due to strong backflow from the ICA.

DISCUSSION

1. KNOWING WHAT SHOULD BE DONE (EVIDENCE)

It is not common in surgery to perform potentially dangerous operations of preventive nature which do not bring immediate benefits to the patient. However, in carotid surgery, it is easy to find scientific evidence on which to rely in surgical decision-making. In addition to the large randomised studies, an enormous number of studies of differing quality have been conducted on carotid surgery. A simple PubMed search with the words "carotid AND surgery" yields almost 36,000 hits. If one spent 10 minutes on every article, it would take 250 days of uninterrupted reading to go through all of them. Moreover, the word "stroke" yields over 160,000 publications, and it would clearly be an impossible task to go through all of these. Luckily, the number of important studies is much smaller, although still large. A fair number of international, national and local guidelines have been published, and although they are based on the same studies, there are still major variations in the interpretation of the studies. Even more variation seems to exist in the interpretation of these guidelines. This is due to the fact that, ultimately, treatment decisions are made between individual surgeons and patients, and there are many non-scientific details, which have not been evaluated in randomised trials, but which also affect decision-making. The fear of stroke makes the patients quite prone to accept the advice given by the treating physician.

In order to make full use of the stroke preventive potential of CEA, continuous efforts to improve the effectiveness, coverage and safety of the practice are needed. An optimal system would identify, catch and treat all the patients whose strokes are preventable, but the reality remains far from this idealistic situation.

We estimated an optimal theoretical number of CEA provision by using existing incidence figures of TIA, minor stroke and age structure of three regions and compared them with the actual provision in these regions: two from public-based health care systems of developed countries with a supposedly well-functioning process, and one from a developing country, where the medical registry was still being improved. None of the systems was optimal. About a half of the patients that should have been operated on were missed both in Finland and the UK, while a much lower proportion of patients had surgery in Egypt. The estimations include an assumption that the actual CEA patients were patients who should be operated on in an optimal situation. It is clear that none of the regions could present an optimal practice, and it is therefore probable that the figures in the comparison, ineffective as they seem, still give too positive a picture of the real situation. As a certain amount of ineffectiveness is always inevitable, the numbers used in planning the service should be higher than the ones in our calculations.

The delay from the first symptom to surgery has been identified as a major source of ineffectiveness. The two- or even one-week target, which is now recommended in guidelines, may actually be too long because after a TIA most of the strokes occur in a shorter period of time (Rothwell et al. 2006, Naylor 2008). Reorganising the patient pathways is an inexpensive way to increase effectiveness. However, there are several rate-limiting steps that must be identified, many of which are common to different areas, but there are also a lot of problems that should be addressed locally. The knowledge gained from how to make the administration of thrombolysis faster in ischaemic stroke could be used in order to cut down the “symptom to knife” time (SKT).

In Scotland, only 51% of 813 patients referred to a TIA clinic were diagnosed as having a TIA (Murray et al. 2007). In order to evaluate which patients should be guided to the fast lane in clinical practice, recognition and stratification tools have been developed. The ABCD2 score, extended recently with infarction, (ABCD2I) provides validated tools to identify a high risk of stroke after TIA in order to prioritise their urgent assessment and treatment (Table 9) (Johnston et al. 2007; Giles et al. 2010). ABCD2 has also been proven to estimate the risk of recurrent stroke severity (Chandratheva et al. 2010). The Face, Arm, Speech Test (FAST) has been used in telephone assessment by emergency call centre and paramedic triage to make stroke thrombolysis possible, so that correct patients could be identified and immediately transported to emergency room consultation (Harbison et al. 2003; Mohd Nor et al. 2004) and an evaluation for thrombolysis.

Table 9. The ABCD2 score to estimate an early risk of stroke after TIA and the severity of stroke.

The patient has a high risk of stroke if the total score is four or higher.
(Johnston et al. 2007; Giles et al. 2010)

Feature	**Points**
Age > 60	1
Blood pressure >140/90	1
Clinical features - Speech disturbance - Unilateral weakness	 1 2
Duration - ≥10 min - ≥1 hour	 1 2
Diabetes	1

In many clinical situations, it can be justified to perform CEA in a less effective situation. If the safety of the operation is locally better than in the randomised studies, patients with a lower risk of stroke, moderate grade stenosis or even asymptomatic patients may be candidates for CEA. Some patients are willing to take the additional risk of surgery with lower expectations for benefit just to eliminate the idea of having a stenotic carotid artery with a risk of stroke or death in the future. The treating physicians bear the responsibility of being aware and sharing with the patients the information on the benefits and hazards of this preventive surgery in different clinical situations. Without knowledge of personal and local results, it remains impossible to give this advice objectively. Despite the abundance of information, there is a continuous need for high quality trials that give more tools both to surgeons and health care providers.

2. KNOWING WHAT HAS BEEN DONE (OUTCOME ANALYSIS)

Continuous critical evaluation of the process and knowledge of the results (outcome analysis) offer an opportunity to improve the process and to prevent more strokes.

Clinical registries provide an opportunity to assess the process and outcome locally and to make comparisons over time and with other published data. A register can provide benchmark indicators for the assessment of treatment and its cost-effectiveness, but the original indicators have not been planned in an optimal way, and changes in register setup may be necessary (e.g. delay times may be needed to be included in the registry data). One advantage of registered data is the great number of procedures which can be analysed. Moreover, patients that would not be included in prospective randomised trials are included, a fact that makes the data more scattered but also more comprehensive. A major concern in using registered data is data validity. It is typical that a registry seems reliable until it is possible to compare it against another register. After cross-matching the registries, several sources of error may be identified and corrected. In Finland, as in most developed countries, several independent registries are kept for health care monitoring purposes (Mähönen et al. 1997; Mähönen et al. 2000; Lepäntalo et al. 2008; Meretoja et al. 2010b). Data of every operated patient are included in several registries, but these registries are not automatically cross-matched. The input process is of key value to the register and should be monitored and audited regularly. For instance, if there are major systematic errors in coding, the value of the registry can be questioned ("garbage in – garbage out"). Without any knowledge about the missing patients, which is a cause of error in registries, it is dangerous to make definite conclusions. On the other hand, the registry is of no use if the systems of data extraction and analysis are not effective. Legislation and data privacy issues may also be obstacles to comprehensive registries, as has been the case with Finnvasc and Karbase (Lepäntalo et al. 1994; Kantonen 1997).

It is possible to use various search criteria for clinical registries such as the HUSVASC dataset. This makes it possible to use the data in various ways, but it also introduces problems in the validity of the search results. If all CEAs are to be included, a combined search should be used to minimise the likelihood of including unrelated operations. If the search does not include any extra patients, some patients will inevitably be missed in the search. On the other hand, if a more simple code-based dataset like the HDR is used, there will be limitations in the possible searches. If a single dataset is retrieved, erroneously coded patients will be missed in the search, and they cannot be retrieved in the future. Moreover, the final search results may include miscoded patients.

We have shown several problems in cross-matching two different registries of HUCH on an individual patient level and came to the conclusion that a simple search, which seems logical, may in fact include many invisible errors. Despite these problems, we found that there were no major systematic differences between the two registries that were compared in the present study. If 90% of the patients are included, the coverage can be considered acceptable. The coverage in both our local registries was good, and the data compared well with the previously published figures from other countries. The perioperative morbidity and mortality rates after CEA compared favourably with the results of major randomised trials and systematic reviews or meta-analyses. We did not identify systematic exclusion of patients with poor outcome, and thus either of our local registries can be used for the identification of true complication rates. The specific vascular registry allowed a more detailed analysis according to indication for surgery. We also found that postoperative complication codes of ICD-9 or ICD-10 coding systems were not used for carotid complications at our hospital. Accordingly, uncritical data utilisation would lead to severe miscalculations. This emphasises the importance of scrutinising registry data and maintaining quality control by conducting occasional random data sample audits as has been previously suggested (Meretoja et al. 2010b).

3. KNOWING WHAT OTHERS DO BETTER (BENCHMARKING)

It is not fruitful to boast about one's excellent results; instead, one should try to understand what one could do better. Moreover, from the perspective of quality improvement, it is not at all rewarding to know if CEA is performed badly somewhere else. Benchmarking means learning from superior performance. It is impossible to compare CEA effectiveness between regions without knowing the quality of the background data and regional reporting standards. Vascunet has taken the first steps towards real European country-wise comparisons in vascular surgery. The problems in comparing two local registries are far less complicated than comparing the results from different countries. Cultural differences, differences in health care provision, differences in population, health economics, data reliability and data input and analysis may hide many important sources of error. Nevertheless, it is informative to compare the available data and to identify questions for future research. The differences between countries may reveal previously unidentified local problems and provide tools to abolish them and to improve patient care. Datasets like Vascunet will also give more specific benchmark tools. The Vascunet registry should include efforts to standardise the reporting of essential parameters. Gradually, with both repetitive reporting and focused audits, a minimum necessary dataset can be defined. This minimum dataset should also include parameters for STK calculations. When it comes to delay, it is interesting to know what solutions others have detected in their efforts to expedite the process. In the near future, it is important that registries should provide reliable delay times regionally, and thus provide a solid foundation for improving the system, including proper resource allocation.

4. KNOWING WHAT CHANGES SHOULD BE DONE (ANALYSIS AND BENCHMARKING)

Several suboptimal details in treatment solutions and processes exist. Delay before CEA has been identified as a major risk factor for stroke after TIA or stroke. When evaluating the effectiveness of the process, shortening the delay would be one of the most effective methods to improve performance. It is far more important than deciding whether to use general or local anaesthesia, CEA or CAS, or the use of patch, which all have been subject to extensive research among other treatment details. On the other hand, no studies have been, or are likely to be, executed in which patient randomisation is based on the timing of surgery. Accordingly, most information is based on post hoc analyses of randomised trials and historical data. A large body of nonrandomised evidence support the fact that TIA and minor stroke patients should be treated urgently and that more 24-hour TIA service clinics should be developed (Johnston et al. 2006; Giles and Rothwell 2007; Lavallee et al. 2007). The introduction of a centralised system is ineffective if patients remain unaware of when and where to seek help. Physician awareness is also an obstacle to the optimisation of patient referral pathways (Hirsch et al. 2001).

Vascular and stroke registers should monitor the delay from symptom to surgery online. This way, it will be possible to identify and address the problem areas and problems in the work-up process. The importance of proper medication in stroke prevention is also crucial. Many series show that patients' medication has a tendency to get worse when some time has passed from a study (Johnson et al. 2007). However, recent data suggest that more and more patients are on optimal or almost optimal medication at the time of TIA or stroke, and thus there may not be much to improve in terms of conservative treatment in a well-organised stroke service (Sairanen et al. 2011).

5. PERFORMING THESE CHANGES (IMPLEMENTATION OF IMPROVEMENTS)

After understanding the need for change, new methods should be developed and implemented. It is often labour- and/or cost-intensive to change the old traditions in health care. On the other hand, some quite simple changes may have a major effect on outcome. For example, from the point of view of costs, it is irrelevant whether a patient is operated within two weeks or within one month, provided that the number of patients and the complication rates remain the same. However, locally at HUCH we saw an 80% increase of CEA operations after implementing the fast-track pathway, and surgery is also performed earlier after TIA or minor stroke (Figure 6.). It is impossible to identify the exact reasons for this, but there have certainly been some improvements in diagnostics and referral pathways, including imaging work-up and the consultation of vascular surgeon already at the neurological emergency room. However, if there is no positive feedback, this increase may be transitional when the initial enthusiasm wanes. Therefore, one should be aware of these major volume changes as soon as possible; otherwise, the whole process may self-destruct in the expansion. Online monitoring and reporting, at least on a yearly basis, provide information about the process for further improvements and decision-making.

Most often, the identified problems are not the only ones that should be addressed. In modern hospital environment, several specialities have their own interests, and these may collide with the changes at hand. For example, it may be difficult to find the increased table time for early surgery and emergency imaging capacity. Close collaboration over specialist boundaries is essential in a high-quality process of care. It is impossible to implement an effective CEA practice without close collaboration amongst all health care professionals from the first patient contact to follow-up. Disease-specific centralisation makes the referral and consultation patterns simple and more effective. A matter that is very difficult to investigate, but is clearly seen in daily practice, is the importance of personal contact between treating physicians. However, standardised order templates along with register monitoring have been shown to have an impact on patient care improvements (California Acute Stroke Pilot Registry (CASPR) Investigators 2005; The AGREE Collaborative Group 2003).

The whole process of care should be planned in a way that supports fast lane diagnostics and treatment. If the target of cutting down the delay from several weeks to one week, and then to 48 hours or faster, is to be reached, then it will also be vital that neurologists and vascular surgeons should physically work in the proximity of each other with adequate resources. Regional education of patients via mass media and primary health care personnel, neurologists, vascular surgeons and all professionals in contact with these patients is key to success. It should also include the fast-lane way of thinking.

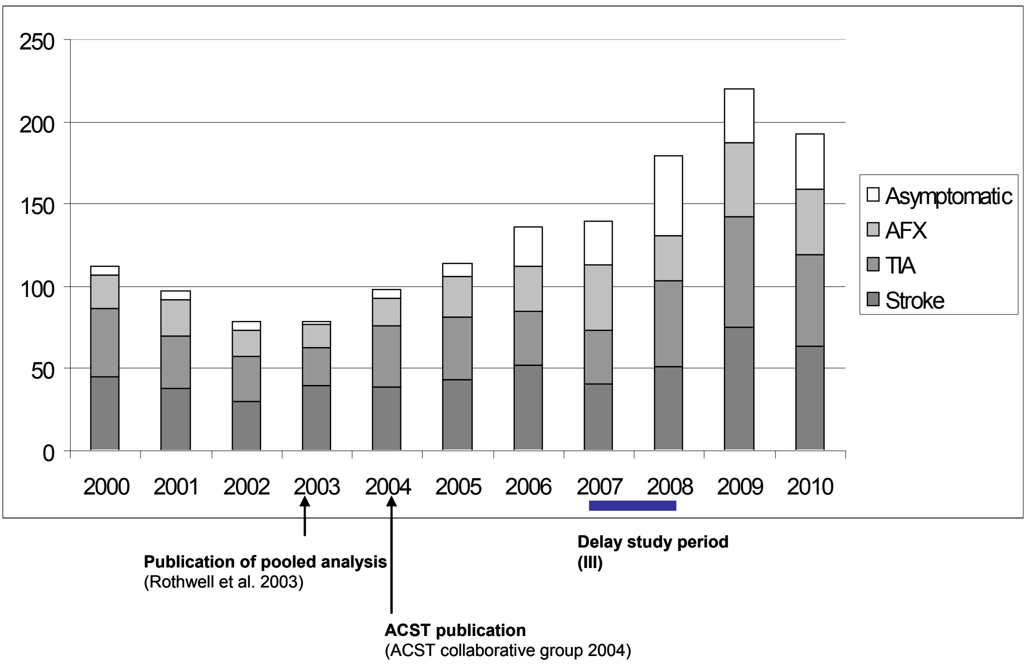
6. KNOWING IF THE CHANGES PERFORMED WERE EFFECTIVE (REANALYSIS)

During outcome analysis and benchmarking, the chosen indicators are tested, and novel quality indicators for analysis can be identified. After the implementation of changes, their success should be subjected to reanalysis, where the information gained from the previous baseline measurements will be compared with data from the updated system to find out if the targets have been reached. During the process, new instruments detected can be used to further improve the quality of the analysis. This reanalysis should be an ongoing audit, which is made possible by continuous registry follow-up (Mehta et al. 2002; CASPR Investigators 2005; Lepäntalo et al. 2008).

It is obvious that data on CEAs performed within, say, 48 hours of the symptoms are still scarce. It seems safe to cut down the SKT to one or two weeks (Salem et al. 2011), but surgery for stroke in evolution or crescendo TIA carries a higher risk (Rerkasem and Rothwell 2009 a). When the delay is shortened to a minimum, the boundary between these different entities gets diluted.

The fact that a study on process structure is performed and its results are critically analysed will inevitably have an effect on the local process of care. This is also one of the reasons why a retrospective method was chosen when planning the study on the delay of carotid surgery. The delay had been identified earlier as one of the main problems in effective CEA provision, but a TIA acute service, that is, a TIA clinic, and extra operation table time was introduced during the study period. This may be seen as an increase in the number of operations in our region (Figure 6.). It is also noteworthy that the proportion of asymptomatic patients did not increase during 2009 and 2010 when the study was actually performed, suggesting that the increase that has been witnessed is a true reflection of the efforts in streamlining the process of care for those with a high risk of stroke. It is difficult or even impossible to know the exact reasons for changes in patient volume. However, the increase seen after 2007 is quite clear and it cannot be explained with aging population, for example. At the same time, a TIA clinic was introduced, but larger numbers of patients were not guided to this practice until late 2010, and it does not seem to explain the increase. However, having a media campaign for laypeople and educating the physicians in health care centres may have had an effect. There was no clear policy change on the emergency admittance of patients. The study was planned because we suspected that the delay was longer than the 2 weeks recommended in the national and international guidelines, which indeed turned out to be the case. We think that it is important to continue the online monitoring of patient flow. Resources should be allocated to this kind of monitoring, and the collaboration between vascular surgeons and neurologists must remain active.

Figure 5. Annual CEA operation figures in HUCH in 2000–2010



7. RESPECTFULLY PUSHING THE LIMITATIONS OF CONVENTIONAL THINKING (INNOVATION AND DEVELOPMENT)

As more operations are performed within hours or few days of the symptoms, new situations will be encountered. More patients will present with floating thrombus and residual thrombus in intracranial arteries. The right approach to these situations remains to be defined, but based on the present data, it seems justified to operate despite fresh thrombus at the bifurcation (Bhatti et al. 2007; Paty et al. 2003; Weis-Müller et al. 2008); however, the operation should perhaps be postponed when intracranial thrombus is seen. More acute occlusions of the arteries will also be seen, but the scientific basis on how to deal with these situations is far less solid than for CEA in most other situations. Promising techniques, such as intraluminal thrombolysis and mechanical thrombectomy, are becoming routine practice, but they are also typically techniques that should be performed within close scientific surveillance, and initially practiced with criticism until evidence from RCTs is available (Baker et al. 2011). In order to achieve continuous improvement in the treatment of these patients close co-operation between vascular surgeons, angioradiologists and neurologists on-call should be available. This kind of service cannot be organised without close 24-hour proximity.

Other reasons for the surgical approach to carotid arteries are not as common as CEA for stroke prevention. Nevertheless, routine CEA gives surgical experience that may also be used in tumour or aneurysm surgery. Traditionally, radical neck surgery comprises radical tumour resection and lymph node dissection. Carotid interposition facilitates more radical surgery in situations where radical excision would otherwise not be possible (McCready et al. 1989; Wright et al. 1996; Muhm et al. 2002; Longo and Kibbe 2005). Head and neck surgeons have routinely use mandibulotomies for the better exposition of the oropharynx (Shaha 1991; Dubner and Spiro 1991; Amin et al. 1999). Combining the experience of different surgical specialists can lead to novel methods of treatment, which would otherwise not be possible, as has also been demonstrated by the innovative team in Marseille (Rosset et al. 2000; Malikov et al. 2010). It is important, however, to identify and accept the limitations of the new techniques introduced. The caseload per surgeon and institution will remain low, and there are clear reasons to centralise these operations nationally and maybe even internationally.

CONCLUSIONS

The full unused potential of stroke prevention by CEA remains to be effectively utilised. Administrative changes in early diagnostics and patient referral pathways making urgent CEA possible would prevent far more strokes than changing small details in the perioperative process itself. The registered data in the HUCH region seem to have reasonable validity and thus give reliable feedback to the treating physicians and information for resource allocation and process planning purposes. The results of the randomised clinical trials provide a solid base for individual treatment planning although the trials do not cover all situations faced at daily practice. Monitoring the results and delay and their reporting should be comprehensive, and the feedback systems should give immediate information for the physicians treating these patients. This information should also be used in resource allocation and regional education on all levels of health care. There are major differences in the effectiveness of the treatment process in different countries. A comparison with other countries should lead both the treating physicians and the decision-makers to critically evaluate and improve their own system.

Standard surgery of the internal carotid artery may be extended to the base of the skull in tumour or aneurysm surgery when there is no other option, but the surgeons should be aware of several options and potential complications. This kind of surgery remains rare and should be centralised to specialised clinics in order to increase the caseload and experience of the treating multidisciplinary team of physicians.

From a thing’s possibility one cannot be certain of its reality.

ACKNOWLEDGEMENTS

This study was carried out at the Department of Vascular Surgery of Helsinki University Central Hospital in 2005-2011.

I wish to especially express my gratitude to the following persons and apologize those whom I forgot.

Mauri, for the planning and supervising of this thesis and even more for your guidance in humanity, respect, friendliness, interest, focusing and vascular surgery. From the first moment I had the honour of meeting you in 1993 as a medical student you have guided me gently through my struggling steps in the medical profession. You have taken me to the most distant places and guided me at home. It has been a privilege to get to know you, not only as a supervisor, but also as a friend. You are a true sensei.

Maarit, for the supervision and help in finalising this work. You have a never-ending ability to find an interest in tables, registers and life. You have an amazing ability to find the positive in everything, and an enviable flexibility. Thank you for mixing your reference frame with mine.

Make and Ari H, for the peer review and valuable comments and discussions. You belong to the few who will have read this thesis.

Ashraf, for your open minded and intelligent ability to teach me the respect in your culture. You helped me to understand the power of history brought into modern life. I wish you can achieve your goals at Assiut and help your people towards a good outcome.

Pekka, for the spectacular scenery, for the metronidazole and for caring. Anders, for showing me how to respect the carotid artery and human tissue. You are a developer and I hope we have many innovative years ahead. Mikael, for fatherly showing me how to respect the person in the patient. I wish you a good rest, please come back soon. Tiina, you had planned the same delay study at the same time, probably before me, which gave me faith. I hope we both got more out of it by putting our thoughts together, I certainly did. Lauri, for your ever-lasting guidance in vascular neurology and for sharing your knowledge with me. Juha-Matti, for the late-hour work and details. Antti, for the long lasting collaboration and for showing me that surgery is mastering the details. Jyrki, for pushing the boundaries and discussing various innovative approaches to the neck.

Professor Thabet for sending Ashraf to us. David and Leif for taking the first hit with the VASCUNET paper. Barry, Erik, Tim, Gabor, Domenico, Thomas and Pius for gathering the data, trusting me and coping with the never-ending flow of e-mails and managing to keep the paper together in spite of the distance. Martin for your friendship and for keeping me from embarrassing myself totally, I hope. You have truly the abilities a professor should have and I am sure your students share my opinion.

Turo for correcting my language (except for the acknowledgements).

Jarmo, Timo and Mikko H for taking pictures and teaching me photography.

Anita for your long lasting experience in science. With all the work you have done to keep us up to date, you should have at least a PhD.

Ilkka, for you being my tutor, for trusting me and for teaching me to deal with difficult situations. I wish I will be privileged to use many more red blood cells with you and to learn from you and with you in the future. Eva, for showing me the greatness in being a teacher and later learning from your student. Mikko J, for sharing carotid surgery, the never ending flow of patients, endless amount of ward rounds and consultation calls. Sani for sharing the sea. Thank you for keeping Lättä on his feet. Sailaritta, for sharing the years of learning and for the continuous ethical considerations. Hold on to your enthusiasm, it makes us others try harder. Eeva-Maija, for your wonderful voice and sparkling personality. Petteri, for your music and the discussions when driving to Tammisaari. Maria, for your sportsmanship, strength and straightforward approach to life. Milla, for your discussing approach. Ivika, for showing the Estonian courage and eagerness. Tiia, for commenting. Karoliina, Katariina, Hanni, Antti and Esa for the prospect of vascular surgery. Aarno for teaching me how to master the three-dimensional surgical wound. Eija for teaching me carotid surgery and tcd.

Kaapo and Tomi for local anesthesia and intelligent questions and answers.

Ari L, for the traumatic experiences. Your discussion skills leave me humble. Thank you for trusting me and guiding me in the world of trauma and surgery. I wish to be able to absorb at least a small part of your knowledge and character. Hannu, for endless discussions on anything from carotid surgery to rum. You have a rare ability to absorb knowledge, but also wisdom. I hope to have many more beers with you. I also wish to find more time for jazz, movies and books. Caj and Reijo for patience. Leo for sharing interest in treating patients, not objects. I wish you return even more skilful than today.

Leena M for your admirable patience when I do not have the HusPlus under control.

Saija, Virpi, Mari, Saara, Anna, Petri, Seija and all other vascular nurses for numerous hours of collaboration and fun.

Irwin for showing me around in the UK, making curry together and sharing your family and life. Alex for showing me your Ukrainian heart.

Rankku for being my friend and being there when difficult. Thank you for being obvious, not someone to please. Something not all of us are privileged to have, a friend for life. I wish never to loose you.

Mamma, for being mother and for your never-ending support, understanding and help. Elias, Pirkko-Liisa, Laila, Tico, Minna, Lea, Markku, Samuel, Krista, Mirjam and your children and families for picking me up when I was lying down. Thank you all for being individuals. You are the best family one can hope for.

Jatta, Heikki, Eero, Ragne, Timo, Tila and your children for your open arms and warmth. Your support has been indispensable.

Tapio for raising me with humanity and philosophy. Thank you for teaching me how to fish and how to respect thinking. Take care of your brain, there is much to loose. Thank you for being my uncle. I promise to find more time for reading.

Nicole for your kindness, William for your affection, Michelle for your joy, Tuomas for the discussions, Lauri for your sisu and Henri for your energy.

Leena for my life and love. You have taught me the meaning of together. With you I have learned to communicate, to express my feelings, to share and to care. You have an unbelievable ability to gently justify assertions and to be systematic. Without you I might not have overcome my anarchy. Thank you for Kaiken.

I hope to be able to always remember and respect
the power of human collaboration.

REFERENCES

Abbott LA, Bladin CF, Levi CR, Chambers BR. What should we do with asymptomatic carotid stenosis? Int J of Stroke 2007;2:27-39.

AbuRahma AF, Copeland SE. Bilateral internal carotic occlusion: natural history and surgical alternatives. Cardiovasc Surg 1998;6:579–583.

The AGREE Collaborative Group. Development and validation of an international appraisal instrument for assessing the quality of clinical practice guidelines: the AGREE project. Qual Saf Health Care 2003;12:18–23.

Aho K. Incidence, profile and early prognosis of stroke. Dissertation, University of Helsinki, Helsinki 1975.

Alexandrov AV. Current and future recanalization strategies for acute ischemic stroke. J Intern Med 2010;267:209–219.

Alimi YS, DiMauro P, Fiacre E, Magnan J, Juhan C. Bluntinjury to the internal carotid artery at the base of the skull: six cases of venous graft restoration. J Vasc Surg 1996;24:249–257.

Amarenco P, Bogousslavsky J, Callahan A III, Goldstein LB, Hennerici M, Rudolph AE, Sillesen H, Simunovic L, Szarek M, Welch KM, Zivin JA; Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators. High-dose atorvastatin after stroke or transient ischemic attack. N Engl J Med 2006;355:549–559.

Amin MR, Deschler DG, Hayden RE. Straight midline mandibulotomy revisited. Laryngoscope 1999;109:1402–1405.

Anzidei M, Napoli A, Zaccagna F, Di Paolo P, Saba L, Cavallo Marincola B, Zini C, Cartocci G, Di Mare L, Catalano C, Passariello R. Diagnostic accuracy of colour Doppler ultrasonography, CT angiography and blood-pool-enhanced MR angiography in assessing carotid stenosis: a comparative study with DSA in 170 patients. Radiol Med 2011 Mar 7. Epub ahead of print.

Attigah N, Külkens S, Zausig N, Hansmann J, Ringleb P, Hakimi M, Eckstein H-H, Allenberg J-R, Böckler D. Surgical therapy of extracranial carotid artery aneurysms: long-term results over a 24-year period. Eur J Vasc Endovasc Surg 2009;37:127–133.

Baker WL, Colby JA, Tongbram V, Talati R, Silverman IE, White CM, Kluger J, Coleman CI. Neurothrombectomy devices for the treatment of acute ischemic stroke: state of the evidence. Ann Intern Med 2011;154:243–252.

Bamford J, Sandercock P, Dennis M, Warlow C, Jones L, McPherson K, Vessey M, Fowler G, Molyneux A, Hughes T, Burn J, Wade D. A prospective study of acute cerebrovascular disease in the community: the Oxfordshire Community Stroke Project 1981–1986. 1. Methodology, demography and incident cases of first-ever stroke. J Neurol Neurosurg Psychiatry 1988;51:1373–1380.

Barnett HJM, Taylor DW, Eliasziw MAM, Fox AJ, Ferguson GG, Haynes RB, R. Rankin RN, Clagett GP, Hachinski VC, Sackett DL, Thorpe KE, Math M, Meldrum HE for the North American Symptomatic Carotid Endarterectomy Trial Collaborators. Benefit of carotid endarterectomy in patients with symptomatic moderate of severe stenosis. N Engl J Med 1998;339:1415–1425.

Bartoli MA, Squarcioni C, Nicoli F, Magnan P-E, Malikov S, Berger L, Lerussi GB, Branchereau A. Early carotid endarterectomy after intravenous thrombolysis for acute ischaemic stroke. Eur J Vasc Endovasc Surg 2009;37:512–518.

Batzdorf U, Gregorius FK. Surgical exposure of the high cervical carotid artery: experimental study and review. Neurosurgery 1983;13:657–661.

Benavente O, Eliasziw M, Streifler JY, Fox AJ, Barnett HJM, Meldrum H for the North American Symptomatic Carotid Endarterectomy Trial Collaborators. Prognosis after transient monocular blindness associated with carotid-artery stenosis. N Engl J Med 2001;345:1084–1090.

Beretta F, Hemida SA, Andaluz N, Zuccarello M, Keller JT. Exposure of the cervical internal carotid artery: surgical steps to the cranial base and morphometric study. Neurosurgery 2006;59(S1):25–34.

Bhatti AF, Leon LR, Labropoulos N, Rubinas TL, Rodriguez H, Kalman P, Schneck M, Psalms SB, Biller, J. Free-floating thrombus of the carotid artery: literature review and case reports. J Vasc Surg 2007;45:199–205.

Boedeker CC, Ridder GJ, Schipper J. Paragangliomas of the head and neck: diagnosis and treatment. Fam Cancer 2005;4:55–59.

Bonati LH, Fraedrich G; Carotid Stenting Trialists' Collaboration. Age modifies the relative risk of stenting versus endarterectomy for symptomatic carotid stenosis - a pooled analysis of EVA-3S, SPACE and ICSS. Eur J Vasc Endovasc Surg 2011;41:153–158.

Bond R, Rerkasem K, Cuffe R, Rothwell PM. A Systematic review of the associations between age and sex and the operative risks of carotid endarterectomy. Cerebrovasc Dis 2005;20:69–77.

Bond R, Rerkasem K, AbuRahma AF, Naylor AR, Rothwell PM. Patch angioplasty versus primary closure for carotid endarterectomy. Cochrane Database Syst Rev 2004;(2):CD000160.

Brothers TE. Initial experience with eversion carotid endarterectomy: absence of a learning curve for the first 100 patients. J Vasc Surg 2005;42:429–434.

Brott TG, Hobson RW 2nd, Howard G, Roubin GS, Clark WM, Brooks W, Mackey A, Hill MD, Leimgruber PP, Sheffet AJ, Howard VJ, Moore WS, Voeks JH, Hopkins LN, Cutlip DE, Cohen DJ, Popma JJ, Ferguson RD, Cohen SN, Blackshear JL, Silver FL, Mohr JP, Lal BK, Meschia JF; CREST Investigators. Stenting versus endarterectomy for treatment of carotid-artery stenosis. N Engl J Med 2010;363:11–23.

Bunch CT, Kresowik TF. Can randomized trial outcomes for carotid endarterectomy be achieved in community-wide practice? Semin Vasc Surg 2004;17:209-213.

California Acute Stroke Pilot Registry (CASPR) Investigators. Prioritizing interventions to improve rates of thrombolysis for ischemic stroke. Neurology 2005;64:654–659.

Cao P, De Rango P, Cieri E, Giordano G. Eversion versus conventional endarterectomy. Semin Vasc Surg 2004;17:236–242.

CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). Lancet 1996;348: 1329–1339.

Cavalcanti DD, Garcia-Gonzalez U, Agrawal A, Tavares PLMS, Spetzler RF, Preul MC. A clear map of the lower cranial nerves at the superior carotid triangle. World Neurosurg 2010;74:188–194.

Chandratheva A, Geraghty OC, Luengo-Fernandez R, Rothwell PM; Oxford Vascular Study. ABCD2 score predicts severity rather than risk of early recurrent events after transient ischemic attack. Stroke 2010;41:851–856.

Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90 056 participants in 14 randomised trials of statins. Lancet 2005;366:1267–1278.

Coccheri S. Asymptomatic carotid stenosis: Natural history and therapeutic implications. Pathophysiol Haemost Thromb 2004;33:298–301.

Coffin O, Maïza D, Galateau-Sallé F, Martel B, Vignon C, Neri E, Derlon JM. Results of surgical management of internal carotid artery aneurysm by the cervical approach. Ann Vasc Surg 1997;11:482–490.

Cohen R, Padilla J, Light D, Diller R. Carotid artery occlusive disease and ocular manifestations: Importance of identifying patients at risk. Optometry 2010;81:359-363.

Cowan JA Jr, Dimick JB, Thompson BG, Stanley JC, Upchurch GR Jr. Surgeon volume as an indicator of outcomes after carotid endarterectomy: an effect independent of specialty practice and hospital volume. J Am Coll Surg 2002;195:814–821.

Crawford RS, Chung TK, Hodgman T, Pedraza JD, Corey M, Cambria RP. Restenosis after eversion vs patch closure carotid endarterectomy. J Vasc Surg 2007;46:41–48.

Crozier JEM, Reid J, Welch GH, Muir KW, Stuart WP. Early carotid endarterectomy following thrombolysis in the hyperacute treatment of stroke. Br J Surg 2011;98:235–238.

Daffertshofer M, Mielke O, Pulswitt A, Felsenstein M, Hennerici M. Transient ischemic attacks are more than “ministrokes”. Stroke 2004;35:2453–2458.

Dennis MS, Bamford JM, Sanderock PA Warlow CP. Incidence of transient ischemic attacks in Oxfordshire, England. Stroke 1989;20:333–339.

Di Carlo A, Lamassa M, Baldereschi M, Pracucci G, Basile AM, Wolfe CDA, Giroud M, Rudd A, Ghetti A, Inzitari D. Sex differences in the clinical presentation, resource use, and 3-month outcome of acute stroke in Europe: Data from a multicenter multinational hospital-based registry. Stroke 2003;34:1114–1119.

Donas KP, Mayer D, Guber I, Baumgartner R, Genoni M, Lachat M. Endovascular repair of extracranial carotid artery dissection: current status and level of evidence. J Vasc Interv Radiol 2008;19:1693–1698.

Dossa C, Shepard AD, Wolford DG, Reddy DJ, Ernst CB. Distal internal carotid exposure: a simplified technique for temporary mandibular subluxation. J Vasc Surg 1990;12:319–325.

DuBose J, Recinos G, Teixeira PG, Inaba K, Demetriades D. Endovascular stenting for the treatment of traumatic internal carotid injuries: expanding experience. J Trauma 2008;65:1561–1566.

Dubner S, Spiro RH. Median mandibulotomy: a critical assessment. Head Neck 1991;13:389–393.

Eckstein HH, Ringled PA, Allenberg J, Berger J, Fraedrich G, Hacke W, Hennerici M, Stingele R, Fiehler J, Zeumer H, Jansen O. Results of the stent-protected angioplasty versus carotid endarterectomy (SPACE) study to treat symptomatic stenoses at 2 years: a multinational prospective, randomized trial. Lancet Neurol 2008;7:893-902.

Ederle J, Bonati LH, Dobson J, Featherstone RL, Gaines PA, Beard JD, Venables GS, Markus HS, Clifton A, Sandercock P, Brown MM; CAVATAS Investigators. Endovascular treatment with angioplasty or stenting versus endarterectomy in patients with carotid artery stenosis in the Carotid And Vertebral Artery Transluminal Angioplasty Study (CAVATAS): long term follow-up of a randomized trial. Lancet Neurol 2009a;8:898–907.

Ederle J, Featherstone RL, Brown MM. Randomized controlled trials comparing endarterectomy and endovascular treatment for carotid artery stenosis: a Cochrane systematic review. Stroke 2009b;40:1373–1380.

Eliason JL, Netterville JL, Guzman RJ, Passman MA, Naslund TC. Skull base resection with cervical-to-petrous carotid artery bypass to facilitate repair of distal internal carotid artery lesions. Cardiovasc Surg 2002;10:31–37.

European Carotid Surgery Trialists' Collaborative Group. Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). Lancet 1998;351:1379–1387.

Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. Endarterectomy for asymptomatic carotid artery stenosis. JAMA 1995;273:1421–1428.

Fazio G, Giovino M, Gullotti A, Bacarella D, Novo G, Novo S. Atherosclerosis, inflammation and Chlamydia pneumoniae. World J Cardiol 2009;31:31–40.

Feigin VL, Lawes CMM, Bennett DA, Anderson CS. Stroke epidemiology: a review of population- based studies of incidence, prevalence, and case-fatality in the late 20th century. Lancet Neurol 2003;2:43–53.

Feigin VL, Lawes CMM, Bennett DA, Barker-Collo SL, Parag V. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. Lancet Neurol 2009;8:355–369.

Ferris G, Roderick P, Smithies A, George S, Gabbay J, Couper N, Chant A. An epidemiological needs assessment of carotid endarterectomy in English health region. Is the need being met? BMJ 1998; 317: 447–451.

Fletcher KE, Underwood W, Davis SQ, Mangrulkar RS, McMahon LF, Saint S. Effects of work hour reduction on residents' lives a systematic review. JAMA 2005;294:1088–1100.

GALA Trial Collaborative Group. General anaesthesia versus local anaesthesia for carotid surgery (GALA): a multicentre, randomised controlled trial. Lancet 2008;372:2132–2142.

Giles MF, Rothwell PM. Risk of stroke early after transient ischaemic attack: a systematic review and meta-analysis. Lancet Neurol 2007;6:1063–1072.

Giles MF, Albers GW, Amarenco P, Arsava MM, Asimos A, Ay H, Calvet D, Coutts S, Cucchiara BL, Demchuk AM, Johnston SC, Kelly PJ, Kim AS, Labreuche J, Lavallee PC, Mas JL, Merwick A, Olivot JM, Purroy F, Rosamond WD, Sciolla R, Rothwell P. Addition of brain infarction to the ABCD2 Score (ABCD2I): a collaborative analysis of unpublished data on 4574 patients. Stroke 2010;41:1907–1913.

Goldemund D, Mikulik R. Reperfusion therapies for acute ischemic stroke. Curr Treat Options Neurol 2010;12:155–166.

Gorlitzer M, Froeschl A, Puschnig D, Locker E, Skyllouriotis P, Meinhart J, Kaucky M, Grabenwoeger M From best evidence to best practice: effective implementation of change in patients' care. Interact CardioVasc Thorac Surg 2009;8:534–537.

Grol R, Grimshaw J. Is the urgent carotid endarterectomy in patients with acute neurological symptoms a safe procedure? Lancet 2003;362:1225–1230.

Halliday A, Lees T, Kamugasha D, Grant R, Hoffman A, Rothwell PM et al. Waiting times for carotid endarterectomy in UK: observational study. BMJ 2009; 338:b1847.

Harbison J, Hossain O, Jenkinson D, Davis J, Louw SJ, Ford GA. Diagnostic accuracy of stroke referrals from primary care, emergency room physicians, and ambulance staff using the face arm speech test. Stroke 2003;34:71–76.

Henriksson M, Lundgren F, Carlsson P. Cost-effectiveness of endarterectomy in patients with asymptomatic carotid artery stenosis. Br J Surg 2008;95:714–720.

Hertzer NR. Extracranial carotid aneurysms: A new look at an old problem. J Vasc Surg 2000;31:823–825.

Hirsch AT, Criqui MH, Treat-Jacobson D, Regensteiner JG, Creager MA, Olin JW, Krook SH, Hunninghake DB, Comerota AJ, Walsh ME, McDermott MM, Hiatt WR. Peripheral arterial disease detection, awareness, and treatment in primary care. JAMA 2001;286:1317–1324.

Hobson RW, Mackey WC, Ascher E, Murad MH, Calligaro KD, Comerota AJ, Montori VM, Eskandari MK, Massop DW, Bush RL, Lal BK, Perler BA. Management of atherosclerotic carotid artery disease: Clinical practice guidelines of the Society for Vascular Surgery. J Vasc Surg 2008;48:480–486.

Holloway RG, Benesch C, Rush SR. Stroke prevention: Narrowing the evidence–practice gap. Neurology 2000;54:1899–1906.

Holt PJE, Poloniecki JD, Loftus M, Thompson MM. Meta-analysis and systematic seview of the relationship between hospital volume and outcome following carotid endarterectomy. Eur J Vasc Endovasc Surg 2007;33:645–651.

International Carotid Stenting Study investigators, Ederle J, Dobson J, Featherstone RL, Bonati LH, van der Worp HB, de Borst GJ, Lo TH, Gaines P, Dorman PJ, Macdonald S, Lyrer PA, Hendriks JM, McCollum C, Nederkoorn PJ, Brown MM. Carotid artery stenting compared with endarterectomy in patients with symptomatic carotid stenosis (International Carotid Stenting Study): an interim analysis of a randomised controlled trial. Lancet 2010;375:985–997.

Joakimsen O, Bønaa KH, Stensland-Bugge E, Jacobsen BK. Age and sex differences in the distribution and ultrasound morphology of carotid atherosclerosis: The Tromsø Study. Arterioscler Thromb Vasc Biol 1999;19:3007–3013.

Johansson EP, Wester P. Delay from symptoms to carotid endarterectomy. J Intern Med 2008; 263:404–411.

Johnson P, Rosewell M, James M. How good is the management of vascular risk after stroke, transient ischaemic attack or carotid endarterectomy? Cerebrovasc Dis 2007;23:156–161.

Johnston SC, Gress DR, Browner WS, Sidney S. Short-term prognosis after emergency department diagnosis of TIA. JAMA 2000;284:2901–2906.

Johnston SC, Nguyen-Huynh MN, Schwarz ME, Fuller K, Williams CE, Josephson SA, Hankey GJ, Hart RG, Levine SR, Biller J, Brown RD Jr, Sacco RL, Kappelle LJ, Koudstaal PJ, Bogousslavsky J, Caplan LR, van Gijn J, Algra A, Rothwell PM, Adams HP, Albers GW. National Stroke Association guidelines for the management of transient ischemic attacks. Ann Neurol 2006;60:301–313.

Johnston SC, Rothwell PM, Nguyen-Huynh MN, Giles MF, Elkins JS, Bernstein AL, Sidney S. Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. Lancet 2007;369:283–292.

Kandil MR, El-Tallawy HN, Farawez HM. Epidemiology of cerebrovascular stroke and TIA in Upper Egypt (Sohag). Relative frequency of stroke in Assiut University Hospital. Egypt J Neurol Psychiatry Neurosurg 2006;43:593–602.

Kantonen I, Lepäntalo M, Salenius JP, Forsström E, Hakkarainen T, Huusari H, Jaakkola A, Kaarne M, Kaartinen P, Kivivuori R, Kostiainen S, Lehtonen J, Loponen P, Luther M, Mäenpää I, Nikula P, Riekkinen H, Rissanen K, Vilkko P, Ylönen K; Finnvasc Study Group. Auditing a nationwide vascular registry--the 4-year Finnvasc experience. Eur J Vasc Endovasc Surg 1997;14:468–474.

Kantonen I, Lepäntalo M, Salenius JP, Mätzke S, Luther M, Ylönen K; The Finnvasc Study Group. Influence of surgical experience on the results of carotid surgery. Eur J Vasc Endovasc Surg 1998;15:155–160.

Kluk J, Grainger S, Nyamekye IK. Is the retrojugular approach safer than the conventional approach for carotid endarterectomy? World J Surg 2009;33:1533–1537.

Kotila M. Incidence, case fatality and outcome of stroke. Dissertation, University of Helsinki, Helsinki 1986.

Krishnaswamy A, Klein JP, Kapadia SR. Clinical Cerebrovascular Anatomy. Catheterization and Cardiovascular Interventions 2010;75:530–539.

Lal BK, Brott TG. The Carotid Revascularization Endarterectomy vs. Stenting Trial completes randomization: lessons learned and anticipated results. J Vasc Surg 2009;50:1224–1231.

Larsen PE, Smead WL. Vertical ramus osteotomy for improved exposure of the distal internal carotid artery: a new technique. J Vasc Surg 1992;15:226–231.

Lasserson DS. Initial management of suspected transient cerebral ischaemia and stroke in primary care: implications of recent research. Postgrad Med J 2009;85:422–427.

Lavallée PC, Meseguer E, Abboud H, Cabrejo L, Olivot J-M, Simon O, Mazighi M, Nifle C, Niclot, P, Lapergue B, Klein IF, Brochet E, Steg PG, Lesèche G, Labreuche J, Touboul P-J, Amarenco P. A transient ischaemic attack clinic with round-the-clock access (SOS-TIA): feasibility and effects. Lancet Neurol 2007;6:953–960.

Law MR, Morris JK, Wald, NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. BMJ 2009;338:b1665.

Leira EC, Changa KC, Davis PH, Clarke WR, Woolson RF, Hansen MD, Adams HP Jr. Can we predict early recurrence in acute stroke? Cerebrovasc Dis 2004;18:139–144.

Lemmens R, Chen F, Ni Y, Fieuws S, Thijs V. Is there a decline in the vascular event rate after transient ischemic attack or stroke in antiplatelet trials? Cerebrovasc Dis 2009;28:439–447.

Lepäntalo M, Salenius JP, Luther M, Ylönen K. Introduction of a population-based vascular registry: validity of data and limitations of registration. The Finnvasc Study Group. Br J Surg 1994;81:979–981.

Lepäntalo M, Venermo M, Laukontaus S, Kantonen I. The role of vascular registries in improving the management of abdominal aortic aneurysm. Scand J Surg 2008; 97:146–153.

Leys D, Kwiecinski H, Bogousslavsky J, Bath P, Brainin M, Diener H-C, Kaste M, Sivenius J, Hennerici MG, Hacke W for the EUSI Executive Committee and the EUSI Writing Committee. Prevention. Cerebrovasc Dis 2004;17(suppl 2):15–29.

Li Z, Chang G, Yao C, Guo L, Liu Y, Wang M, Liu D, Wang S. Endovascular stenting of extracranial carotid artery aneurysm: A systematic review. Eur J Vasc Endovasc Surg 2011;42:419-425.

Liapis CD, Bell PRF, Mikhailidis, Sivenius J, Nicolaides A, Fernandes e Fernandes J, Biasi G, Norgren L, on behalf of the ESVS Guidelines Collaborators. ESVS Guidelines. Invasive treatment for carotid stenosis: indications, techniques. Eur J Vasc Endovasc Surg 2009;37:1–19.

Longo GM, Kibbe MR. Aneurysms of the carotid artery. Semin Vasc Surg 2005;18:178–183.

Luengo-Fernandez R, Gray AM, Rothwell PM. Effect of urgent treatment for transient ischaemic attack and minor stroke on disability and hospital costs (EXPRESS study): a prospective population-based sequential comparison. Lancet Neurol 2009;8:235–243.

Lusis AJ. Atherosclerosis. Nature 2000;407:233–241.

Lutz HJ, Michael R, Gahl B, Savolainen H. Is carotid endarterectomy a trainee operation? World J Surg 2009;33:242–245.

Lutz HJ, Sacuiu RD, Gahl B, Savolainen H. Best medical therapy or wishful thinking in carotid disease? A single-centre audit in Germany. Eur J Vasc Endovasc Surg 2011;41:501–506.

Lyden P, Brott T, Tilley B, Welch KM, Mascha EJ, Levine S, Haley EC, Grotta J, Marler J. Improved reliability of the NIH Stroke Scale using video training. NINDS TPA Stroke Study Group. Stroke 1994;25:2220–2226.

Malikov S, Thomassin JM, Magnan PE, Keshelava G, Bartoli M, Branchereau A. Open surgical reconstruction of the internal carotid artery aneurysm at the base of the skull. J Vasc Surg 2010;51:323–329.

Mantese VA, Timaran CH, Chiu D, Begg RJ, Brott TG; CREST Investigators. The Carotid Revascularization Endarterectomy versus Stenting Trial (CREST): stenting versus carotid endarterectomy for carotid disease. Stroke 2010;41:S31–34.

Marnane M, Duggan CA, Sheehan OC, Merwick A, Hannon N, Curtin D, Harris D, Williams EB, Horgan G, Kyne L, McCormack PME, Duggan J, Moore A, Crispino-O'Connell G, Kelly PJ. Stroke subtype classification to mechanism-specific and undetermined categories by TOAST, A-S-C-O, and causative classification system: direct comparison in the North Dublin Population Stroke Study. Stroke 2010;41:1579–1586.

Mas JL, Chatellier G, Beyssen B, Branchereau A, Moulin T, Becquemin JP, Larrue V, Lièvre M, Leys D, Bonneville JF, Watelet J, Pruvo JP, Albucher JF, Viguier A, Piquet P, Garnier P, Viader F, Touzé E, Giroud M, Hosseini H, Pillet JC, Favrole P, Neau JP, Ducrocq X; EVA-3S Investigators. Endarterectomy versus stenting in patients with symptomatic severe carotid stenosis. NEJM 2006;355:1660–1671.

Mayberg MR, Wilson SE, Yatsu F, Weiss DG, Messina L, Hershey LA, Colling C, Eskridge J, Deykin D, Winn HR. Carotid endarterectomy and prevention of cerebral ischemia in symptomatic carotid stenosis. Veterans Affairs Cooperative Studies Program 309 Trialist Group. JAMA 1991;266:3289–3294.

McCready RA, Miller SK, Hamaker RC, Singer MI, Herod GT. What is the role of carotid resection in the management of advanced cervical cancer? J Vasc Surg 1989;10:274–280.

McPherson CM, Woo D, Cohen PL, Pancioli AM, Kissela BM, Carrozzella JA, Tomsick TA, Zuccarello M, Chaturvedi S. Early carotid endarterectomy for critical carotid artery stenosis after thrombolysis therapy in acute ischemic stroke in the middle cerebral artery. Editorial comment. Stroke 2001;32:2075-2080.

Mead GE, Lewis SC, Wardlaw JM, Dennis MS. Comparison of risk factors in patients with transient and prolonged eye and brain ischemic syndromes. Stroke 2002;33:2383–2390.

Mehta RH, Montoye CK, Gallogly M, Baker P, Blount A, Faul J, Roychoudhury C, Borzak S, Fox S, Franklin M, Freundl M, Kline-Rogers E, LaLonde T, Orza M, Parrish R, Satwicz M, Smith MJ, Sobotka P, Winston S, Riba AA, Eagle KA, for the GAP Steering Committee of the American College of Cardiology. Improving quality of care for acute myocardial infarction. The Guidelines Applied in Practice (GAP) initiative. JAMA. 2002;287:1269–1276.

Meier P, Knapp G, Tamhane U, Chaturvedi S, Gurm HS. Short term and intermediate term comparison of endarterectomy versus stenting for carotid artery stenosis: systematic review and meta-analysis of randomised controlled clinical trials. BMJ 2010;340:c467.

Meretoja A, Roine RO, Kaste M, Linna M, Juntunen M, Erilä T, Hillbom M, Marttila R, Rissanen A, Sivenius J, Häkkinen U. Effectiveness of primary and comprehensive stroke centers. PERFECT Stroke: A nationwide observational study from Finland. Stroke 2010 a;41:1102–1107.

Meretoja A, Roine RO, Kaste M, Linna M, Roine S, Juntunen M, Erilä T, Hillbom M, Marttila R, Rissanen A, Sivenius J, Häkkinen U. Stroke monitoring on a national level: PERFECT Stroke, a comprehensive, registry-linkage stroke database in Finland. Stroke 2010 b;41:2239-2246.

Mock CN, Lilly MP, McRae RG, Carney WI Jr. Selection of the approach to the distal internal carotid artery from the second cervical vertebra to the base of the skull. J Vasc Surg 1991;13:846–853.

Mohd Nor A, McAllister C, Louw SJ, Dyker AG, Davis M, Jenkinson D, Ford GA. Agreement between ambulance paramedic- and physician-recorded neurological signs with Face Arm Speech Test (FAST) in acute stroke patients. Stroke 2004;35:1355–1359.

Muhm M, Grasl MCh, Burian M, Exadaktylos A, Staudacher M, Polterauer P. Carotid resection and reconstruction for locally advanced head and neck tumors. Acta Otolaryngol. 2002;122:561–564.

Murray S, Bashir K, Lees KR, Muir K, MacAlpine C, Roberts M, Langhorne P. Epidemiological aspects of referral to TIA clinics in Glasgow. Scott Med J 2007;52:4–8.

MRC Asymptomatic Carotid Surgery Trial Collaborative Group. Management of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial. Lancet 2004;363:1491–1502.

Mähönen M, Salomaa V, Brommels M, Molarius A, Miettinen H, Pyörälä K, Tuomilehto J, Arstila M, Kaarsalo E, Ketonen M, Kuulasmaa K, Lehto S, Mustaniemi H, Niemelä M, Palomäki P, Torppa J, Vuorenmaa T. The validity of hospital discharge register data on coronary heart disease in Finland. Eur J Epidemiol 1997;13:403–415.

Mähönen M, Salomaa V, Keskimäki I, Moltchanov V, Torppa J, Molarius A, Tuomilehto J, Sarti C; FINMONICA Stroke Register Study group. The feasibility of combining data from routine Hospital Discharge and Causes-of-Death Registers for epidemiological studies on stroke. Eur J Epidemiol 2000;16:815–817.

Nair R, Robbs JV, Naidoo NG. Spontaneous carotid aneurysms. Br J Surg 2000;87:186-190.

Naylor AR. An update on the randomised trials of interventions for symptomatic and asymptomatic carotid artery disease. J Vasc Endovasc Surg 2006;13:111–120.

Naylor AR. Delay may reduce procedural risk, but at what price to the patient? Eur J Vasc Endovasc Surg 2008;35:383–391.

Naylor AR, Gaines PA, Rothwell PM. Who benefits most from intervention for asymptomatic carotid stenosis: patients or professionals? Eur J Vasc Endovasc Surg 2009;37:625–632.

Nazarian SM, Yenokyan G, Thompson RE, Griswold ME, Chang DC, Perler BA. Statistical modeling of the volume-outcome effect for carotid endarterectomy for 10 years of a statewide database. J Vasc Surg 2008;48:343–350.

Nicolaides AN, Kakkos SK, Kyriacou E, Griffin M, Sabetai M, Thomas DJ, Tegos T, Geroulakos G, Labropoulos N, Dore CJ́, Morris TP, Naylor R, Abbott AL, for the Asymptomatic Carotid Stenosis and Risk of Stroke (ACSRS) Study Group,. Asymptomatic internal carotid artery stenosis and cerebrovascular risk stratification. J Vasc Surg 2010;52:1486–1496.

North American Symptomatic Carotid Endarterectomy Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. N Engl J Med 1991; 325:445–453.

Nouraei SA, Al-Rawi PG, Sigaudo-Roussel D, Giussani DA, Gaunt ME. Carotid endarterectomy impairs blood pressure homeostasis by reducing the physiologic baroreflex reserve. J Vasc Surg 2005;41:631–637.

Numminen H, Kotila M, Waltimo O, Aho K, Kaste M. Declining incidence and mortality rates of stroke in Finland from 1972 to 1991. Results of three population-based stroke registers. Stroke 1996;27:1487–1491.

O'Hara PJ, Hertzer NR, Mascha EJ, Krajewski LP, Clair DG, Ouriel K. A prospective, randomized study of saphenous vein patching versus synthetic patching during carotid endarterectomy. J Vasc Surg 2002;35:324–330.

Olin JW, Sealowe BA. Diagnosis, management, and future developments of fibromuscular dysplasia. J Vasc Surg 2011;53:826-836.

Paty PSK, Adeniyi JA, Mehta M, Darling C III, Chang BB, Kreienberg PB, Ozsvath KJ, Roddy SP, Shah DM. Surgical treatment of internal carotid artery occlusion. J Vasc Surg 2003;37:785–788.

Pavlovic AM, Barras CD, Hand PJ, Tress BM, Desmond PM, Davis SM. Brain imaging in transient ischemic attack – redefining TIA. J Clin Neurosci 2010;17: 1105–1110.

Persoon S, Klijn CJM, Algra A, Kappelle J.L Bilateral carotid artery occlusion with transient or moderately disabling ischaemic stroke: clinical features and long-term outcome. J Neurol 2009;256:1728–1735.

Ploeg AJ, Flu HC, Lardenoye JHP, Hamming JF, Breslau PJ. Assessing the quality of surgical care in vascular surgery; moving from outcome towards structural and process measures. Eur J Vasc Endovasc Surg 2010; 40:696–707.

Poisson SN, Johnston SC, Sidney S, Klingman JG, Nguyen-Huynh MN. Gender differences in treatment of severe carotid stenosis after transient ischemic attack. Stroke 2010;41:1891–1895.

Poisson S, Johnston SC. Prevention of stroke following transient ischemic attack. Curr Atheroscler Rep 2011;13:330-337.

Pritz MB. Timing of carotid endarterectomy after stroke. Stroke 1997;28:2563–2567.

Rectenwald JE, Upchurch GR Jr, Arbor A. Impact of outcomes research on the management of vascular surgery patients. J Vasc Surg 2007;45:131A–140A.

Redekop GJ. Extracranial carotid and vertebral artery dissection: a review. Can J Neurol Sci 2008;35:146-152.

Rerkasem K, Rothwell PM. Systematic review of the operative risks of carotid endarterectomy for recently symptomatic stenosis in relation to the timing of surgery. Stroke 2009 a;40:e564-572.

Rerkasem K, Rothwell PM. Patch angioplasty versus primary closure for carotid endarterectomy. Cochrane Database Syst Rev Update. 2009 b;4:CD00160.

Rerkasem K, Rothwell PM. Local versus general anaesthesia for carotid endarterectomy. Cochrane Database of Systematic Reviews 2009 c, 3, 1–23.

Ricotta JJ 2nd, Malgor RD. A review of the trials comparing carotid endarterectomy and carotid angioplasty and stenting. Perspect Vasc Surg Endovasc Ther 2008;20:299–308.

Riles TS, Lamparello PJ, Giangola G, Imparato AM. Rupture of the vein patch: a rare complication of carotid endarterectomy. Surgery 1990;107:10–12.

Rissanen A. Cerebrovascular disease in the Jyväskylä region, Central Finland. Dissertation, Department of Neurology, University of Kuopio 1992; Series of Reports No. 23.

Rosamond W, Flegal K, Friday G, Furie K, Go A, Greenlund K, Haase N, Ho M, Howard V, Kissela B, Kittner S, Lloyd-Jones D, McDermott M, Meig, Moy C, Nichol G, O'Donnell CJ, Roger V, Rumsfeld J, Sorlie P, Steinberger J, Thom T, Wasserthiel-Smoller S, Hong Y for the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2007 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2007;115:e69-e171.

Ross R. Atherosclerosis—an inflammatory disease. N Engl J Med 1999;340:115–126.

Rosset E, Albertini J-N, Magnan PE, Ede B, Thomassin JM, Branchereau A. Surgical treatment of extracranial internal carotid artery aneurysms. J Vasc Surg 2000;31:713–723.

Rothwell PM, Eliasziw M, Gutnikov SA, Fox AJ, Taylor DW, Mayberg MR, Warlow CP, Barnett HJM for the Carotid Endarterectomy Trialists' Collaboration. Analysis of pooled data from the randomised controlled trials of endarterectomy for symptomatic carotid stenosis. Lancet 2003; 361:107–116.

Rothwell PM, Eliasziw M, Gutnikov SA, Warlow CP, Barnett HJ; Carotid Endarterectomy Trialists Collaboration. Endarterectomy for symptomatic carotid stenosis in relation to clinical subgroups and timing of surgery. Lancet 2004 a;363:915–924.

Rothwell PM, Eliasziw M, Gutnikov SA, Warlow CP, Barnett HJM. Sex difference in the effect of time from symptoms to surgery on benefit from carotid endarterectomy for transient ischemic attack and nondisabling stroke. Stroke 2004 b;35:2855–2861.

Rothwell PM, Goldstein LB. Carotid endarterectomy for asymptomatic carotid stenosis: Asymptomatic Carotid Surgery Trial. Stroke 2004;35:2425–2427.

Rothwell PM, Buchan A, Johnston SC. Recent advances in management of transient ischaemic attacks and minor ischaemic strokes. Lancet Neurol 2006;5:323–331.

Rothwell PM, Giles MF, Chandratheva A, Marquardt L, Geraghty O, Redgrave JNE, Lovelock CE, Binney LE, Bull LM, Cuthbertson FC, Welch SJV, Bosch S, Carasco-Alexander F, Silver LE, Gutnikov SA, Mehta Z on behalf of the Early use of Existing Preventive Strategies for Stroke (EXPRESS) study. Effect of urgent treatment of transient ischaemic attack and minor stroke on early recurrent stroke (EXPRESS study): a prospective population-based sequential comparison. Lancet 2007;370:1432–1442.

Rubin BG. Impact of plaque characterization on carotid interventions. Perspect Vasc Surg Endovasc Ther 2006;18:312–315.

Rudarakanchana N, Dialynas M, Halliday A. Asymptomatic Carotid Surgery Trial-2 (ACST-2): rationale for a randomised clinical trial comparing carotid endarterectomy with carotid artery stenting in patients with asymptomatic carotid artery stenosis. Eur J Vasc Endovasc Surg 2009;38:239–242.

Russell DA, Gough MJ. Intracerebral haemorrhage following carotid endarterectomy. Eur J Vasc Endovasc Surg 2004;28:115–123.

Saikku P, Leinonen M, Mattila K, Ekman MR, Nieminen MS, Makela PH, Huttunen JK, Valtonen V. Serological evidence of an association of a novel chlamydia, TWAR, with chronic coronary heart disease and acute myocardial infarction. Lancet 1988;2:983–986.

Sairanen T, Vikatmaa P, Lindholm JM, Tatlisumak T. Medical treatment of carotid endarterectomy patients requires attention. 2011, Acta Neurol Scand;submitted.

Sajid MS, Hamilton G, Baker DM on behalf of Joint Vascular Research Group. A multicenter review of carotid body tumour management. Eur J Vasc Endovasc Surg 2007;34:127–130.

Salem MK, Sayers RD, Bown MJ, Eveson DJ, Robinson TG, Naylor AR. Rapid access carotid endarterectomy can be performed in the hyperacute period without a significant increase in procedural risks. Eur J Vasc Endovasc Surg 2011;41:222–228.

Salenius JP. National vascular registry in Finland--FINNVASC. FINNVASC Study Group. Ann Chir Gynaecol 1992;81:257–260.

Shaha AR. Mandibulotomy and mandibulectomy in difficult tumors of the base of the tongue and oropharynx. Semin Surg Oncol 1991;7:25–30.

Schwamm L, Reeves MJ, Frankel M. Designing a sustainable national registry for stroke quality improvement. Am J Prev Med 2006;31:S251–S257.

Scott EW, Dolson L, Day AL, Seeger JM. Carotid endarterectomy complicated by vein patch rupture. Neurosurgery 1992; 31:373–377.

Sillesen H. What does ‘best medical therapy’ really mean? Eur J Vasc Endovasc Surg 2008;35:139–144.

Sivenius J. Studies on the rehabilitation, epidemiology and clinical features of stroke in East Central Finland. Dissertation, Department of Neurology, University of Kuopio 1982; Series of Reports No. 6.

Sivenius J, Torppa J, Tuomilehto J, Immonen-Räihä P, Kaarisalo M, Sarti C, Kuulasmaa K, Mähönen M, Lehtonen A, Salomaa V. Modelling the burden of stroke in Finland until 2030. International Journal of Stroke 2009;4:340–345.

Sivenius J, Torppa J, Tuomilehto J, Immonen-Räihä P, Kaarisalo M, Sarti C, Kuulasmaa K, Mähönen M, Lehtonen A, Salomaa V. Aivohalvausten ilmaantuvuuden kehityssuunnat Suomen väestössä vuoteen 2030 (Trends in the stroke incidence in the Finnish population). Suom Lääkäril 2010;65:1699–1704.

Stehr A, Scodacek D, Wustrack H, Steinbauer M, Töpel I, Pfister K, Kasprzak PM Retrojugular versus ventrojugular approach to carotid bifurcation for eversion endarterectomy: a prospective randomized trial. Eur J Vasc Endovasc Surg 2008;35:190–195.

Stoneham MD, Thompson JP. Arterial pressure management and carotid endarterectomy. Br J Anaesth 2009;102:442–452.

Streifler JY, Eliasziw M, Benavente OR, Harbison JW, Hachinski VC, Barnett HJM, Simard D. The risk of stroke in patients with first-ever retinal vs hemispheric transient ischemic attacks and high-grade carotid stenosis. Arch Neurol 1995;52:246–249.

Swedvasc report 2010: Nationella kvalitetsregistret för kärlkirurgi Årsrapport 2010 (verksamhetsåret 2009): 5–9. www.ucr.uu.se/swedvasc.

The Swedish national registry for vascular surgery, Swedvasc. Annual report 2011 (Activities in 2010): 8-11. www.ucr.uu.se/swedvasc.

van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. Stroke 1988;19:604–607.

Tu JV, Willison DJ, Silver FL, Fang J, Richards JA, Laupacis A, Kapral MK; Investigators in the Registry of the Canadian Stroke Network Impracticability of informed consent in the Registry of the Canadian Stroke Network. N Engl J Med. 2004;350:1414–1421.

Troeng T, Malmstedt J, Björck M. External validation of the Swedvasc registry: a first-time individual cross-matching with the unique personal identity number. Eur J Vasc Endovasc Surg 2008;36:705–712.

Turtzo LC, McCullough LD. Sex differences in stroke. Cerebrovasc Dis 2008;26:462–474.

Vikatmaa P, Lajunen T, Ikonen TS, Pussinen PJ, Lepäntalo M, Leinonen M, Saikku P. Chlamydial lipopolysaccharide (cLPS) is present in atherosclerotic and aneurysmal arterial wall-cLPS levels depend on disease manifestation. Cardiovasc Pathol 2010;19:48–54.

Walker LJ, Ismail A, McMeekin W, Lambert D, Mendelow AD, Birchall D. Computed tomography angiography for the evaluation of carotid atherosclerotic plaque: correlation with histopathology of endarterectomy specimens. Stroke 2002;33:977–981.

Wardlaw JM, Murray V, Berge E, del Zoppo GJ. Thrombolysis for acute ischaemic stroke. Cochrane Database of Systematic Reviews 2009, Iss 4,1–81.

Weimar C, Goertler M, Harms L, Diener H-C for the German Stroke Study Collaboration. Distribution and outcome of symptomatic stenoses and occlusions in patients with acute cerebral ischemia. Arch Neurol 2006;63:1287–1291.

Weis-Müller BT, Huber R, Spivak-Dats A, Turowski B, Siebler M, Sandmann W. Symptomatic acute occlusion of the internal carotid artery: reappraisal of urgent vascular reconstruction based on current stroke imaging. J Vasc Surg 2008;47:752–759.

Wennberg DE, Lucas FL, Birkmeyer JD, Bredenberg CE, Fisher ES. Variation in carotid endarterectomy mortality in the Medicare population. Trial hospitals, volume, and patient characteristics. JAMA 1998;279:1278–1281.

Wolintz RJ. Carotid endarterectomy for ophthalmic manifestations: is it ever indicated? J Neuro-Ophthalmol 2005;25:299–302.

Working group appointed by The Finnish Medical Society Duodecim and Finnish Neurological Society. Update on current care guidelines: cerebral infarction (stroke). Duodecim 2011;127:500–501. Finnish.

Wright JG, Nicholson R, Schuller DE, Smead WL. Resection of the internal carotid artery and replacement with greater saphenous vein: a safe procedure for en bloc cancer resections with carotid involvement. J Vasc Surg 1996;23:775–782.

Wu CM, McLaughlin K, Lorenzetti DL, Hill MD, Manns BJ, Ghali WA. Early risk of stroke after transient ischemic attack: a systematic review and meta-analysis. Arch Intern Med 2007;167:2417–2422.